Application Type	Efficacy Supplement
STN	125324/767
CBER Received Date	March 28, 2012
PDUFA Goal Date	January 26, 2013
Division / Office	DVRPA / OVRR
Priority Review	No
Reviewer Name	Tina Khoie Mongeau, M.D., M.P.H.
Review Completion Date / Stamped Date	January 24, 2013
Supervisory Concurrence	Jeffrey Roberts, M.D., Branch Chief
Applicant	Wyeth Pharmaceuticals Inc.
Established Name	Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)
(Proposed) Trade Name	Prevnar 13
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc	Each 0.5 mL dose contains ~ 2.2 ug of each capsular saccharide for *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4 ug of serotype 6B; ~ 34 ug CRM_{197} carrier protein; 295 µg succinate buffer (5mM), 125 µg aluminum as $AlPO_4$ adjuvant, and 100 µg polysorbate 80 (0.02%).
Dosage Form(s) and Route(s) of Administration	0.5 mL suspension for intramuscular injection, supplied in a single dose pre-filled syringe
Dosing Regimen	A single dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of invasive pneumococcal disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F and active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in children 6 through 17 years of age.

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ANCOVA	Analysis of Covariance
AOM	Acute Otitis Media
BLA	Biologics License Application
sBLA	Biologics License Application supplement
CAP	Community Acquired Pneumonia
CAPITA	Community Acquired Pneumonia Immunization Trial in Adults
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CFR	Code of Federal Regulations
CRF	Case Report Form
CRM	Cross Reacting Material
CSR	Clinical Study Report
ELISA	Enzyme Linked Immunosorbent Assay
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition Assay
ICF	Informed Consent Form
IgG	Immunoglobulin G
IPD	Invasive Pneumococcal Disease
LL	Lower Limit
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
NCKP	Northern California Kaiser Permanente
OM	Otitis Media
OPA	Opsonophagocytic Antibody
P80	Polysorbate 80
PCV	Pneumococcal Conjugate Vaccine
PCV7	Prevnar
PCV13	Prevnar 13
PeRC	Pediatric Review Committee
PI	Package Insert
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

STN	Submission Tracking Number
TIV	Trivalent Inactivated Influenza Vaccine
US	United States
VRBPAC	Vaccine and Related Biological Products Advisory Committee
PPSV23	23-valent pneumococcal polysaccharide vaccine

1. EXECUTIVE SUMMARY

Wyeth Pharmaceuticals Inc. has submitted a Biologics License Application supplement (sBLA) to support the use of a single dose of Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein] (Prevnar 13) in children 6 through 17 years of age. The proposed indications in this age group are the active immunization for the prevention of invasive pneumococcal disease caused by the thirteen *Streptococcus pneumoniae* serotypes contained in the vaccine and the active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The approval of Prevnar 13 (PCV13) for use in children and adolescents 6 through 17 years of age would be based on an approach in which vaccine effectiveness against invasive pneumococcal disease (IPD) is inferred from immunologic parameters. This is similar to the approach for the clinical development of PCV13 for use in infants and young children up through 5 years of age. The catch-up immunization schedule for previously unvaccinated children 7 months through 5 years of age was also supported by immune response data.

The safety and effectiveness of Prevnar 13 in children 6 through 17 years of age was evaluated in a single clinical study (study 6096A1-3011) to support expanded use of the vaccine in this age group. Study 3011 was a phase 2/3, nested exploratory, non-randomized, multicenter study in which approximately 300 subjects were enrolled into each of 4 study groups based on age at enrollment. Data from study groups 1 and 2, which included children ≥ 15 months to < 5 years of age, were included in the original Biologics License Application (BLA) to support a supplemental dose of Prevnar 13 among children who completed the 4-dose Prevnar (PCV7) series and are described in the Prevnar 13 package insert. The evaluation of Prevnar 13 safety and immunogenicity in groups 3 and 4, which included subjects ≥ 5 to < 18 years of age, is considered to be the “age-expansion” study and is a deferred postmarketing requirement under the Pediatric Research Equity Act (PREA). Immunogenicity data from the first 100 subjects enrolled into each of groups 3 and 4 (the exploratory cohort) were used to establish the primary endpoint and criteria for testing in the confirmatory cohort (the next 200 subjects enrolled in each of groups 3 and 4).

The primary study objective for children 5 through 9 years of age was to demonstrate non-inferiority of the serotype-specific immune responses induced by PCV13, as measured by an IgG enzyme-linked immunosorbent assay (ELISA) one month after vaccination, compared to the IgG geometric mean concentrations (GMCs) one month after the fourth study vaccination from a historical control group from study 6096A1-3005 (study 3005). Study 3005 supported the initial licensure of Prevnar 13 for use in children 6 weeks through 5 years of age); the historical control group was comprised of both Prevnar (PCV7) recipients from study 3005 for the 7 common serotypes and PCV13

recipients (combined PCV13 lot groups) from study 3005 for the 6 additional serotypes. The primary objective for children 10 through 17 years of age was to demonstrate non-inferiority of the serotype-specific immune responses induced by a single dose of PCV13, as measured by an opsonophagocytic activity (OPA) assay one month after vaccination, compared to the OPA antibody geometric mean titers (GMTs) achieved by 5 through 9 year olds one month after vaccination in the same study.

A total of 182 children 5 through 9 year olds and 190 children 10 through 17 year olds were included in the evaluable (per-protocol) immunogenicity populations for the confirmatory cohorts. The primary effectiveness (immunogenicity) endpoints were met for each of the thirteen vaccine serotypes for children 5 through 9 years of age and for 12 of the 13 vaccine serotypes for children 10 through 17 years of age (except serotype 3). The IgG GMCs induced by PCV13 among children 5 through 9 year olds were shown to be non-inferior to the post-dose 4 IgG GMCs among PCV7 recipients in study 3005 for the 7 common serotypes and among PCV13 recipients in study 3005 for the 6 additional serotypes (Tables 9 and 10, page 28). The non-inferiority criterion required that the GMC ratio (study 3011/study 3005) for each of the 13 serotypes be greater than 0.5 (i.e., lower limit of the 2-sided 95% confidence interval (CI) for the GMC ratio > 0.5). For children 10 through 17 years of age, the OPA antibody GMTs were shown to be non-inferior to the OPA antibody GMTs achieved among PCV13 recipients 5 through 9 years of age in study 3011 for 12 of the 13 vaccine serotypes (except serotype 3) (Table 11, page 29). The non-inferiority criterion required that the GMT ratio (10 thru 17 yr olds / 5 thru 9 yr olds) be greater than 0.5 (i.e., lower limit of the 2-sided 95% CI for the GMT ratio > 0.5) for each of the 13 serotypes. The non-inferiority criterion was missed by a small margin for serotype 3 (lower 95% CI of 0.48).

A total of 294 children 5 through 9 year olds and 298 children 10 through 17 years olds were included in the safety population (which included subjects enrolled into both the exploratory and confirmatory study cohorts). Safety parameters evaluated in each study included unsolicited adverse events (AEs) and pre-specified solicited AEs (local injection site reactions and systemic AEs). The most common solicited local reaction was injection site tenderness, with nearly 20% of 5 through 9 year olds and 44% of 10 through 17 years olds experiencing significant tenderness (defined as limitation of arm movement). These rates of significant tenderness are comparable to rates observed with some routine pediatric vaccines administered to children in this age group, such as Boostrix (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) and Gardasil (Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant). The most common solicited systemic AEs included irritability, increased sleep and decreased appetite. There were no reported deaths, no adverse events that resulted in withdrawal from the study, and no serious adverse events which were considered related to the study vaccination during the study period.

For the purposes of PREA, the pediatric population includes children from birth through 16 years of age. The Applicant previously received a waiver for PREA requirements to evaluate prevention of otitis media in children 6 through 16 years of age, because the product failed to represent a meaningful therapeutic benefit over existing therapies

(antibiotic therapy) for pediatric patients in this age group and it is unlikely to be used in a substantial number of children 6 through 16 years of age due to the low incidence of otitis media in this age group. For the IPD and otitis media indications, studies in children from birth to < 6 weeks of age were waived, and studies in children 6 weeks through 5 years of age have been completed. Thus, the pediatric study requirement in children 6 through 16 years of age was deferred for the IPD indication. Although this deferred study, study 3011, was only required to enroll children 6 through 16 years of age, the Applicant chose to enroll children 5 through 17 years of age.

Submission of this supplement, which contains the final report of deferred pediatric study 3011 to evaluate the safety and immunogenicity of Prevnar 13 in pediatric patients 6 through 16 years of age, fulfills the single post-marketing requirement (PMR) under PREA specified in the February 24, 2010 approval letter for the original Prevnar 13 BLA. A presentation of the results of the age expansion component of study 3011 was made to the FDA Pediatric Review Committee (PeRC) on December 12, 2012. The Committee concurred that the PMR for this study is fulfilled. PREA does not otherwise apply to this application, as this application does not provide for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

The available safety and immunogenicity data from 5 through 17 year olds in study 6096A1-3011 support the approval of Prevnar 13 in children 6 through 17 years of age for the prevention of invasive pneumococcal disease caused by the serotypes contained in the vaccine. With regards to the proposed otitis media indication, the immunogenicity comparisons in study 3011 to the post-dose 4 immune responses in study 3005 are not applicable to the determination of protection against disease endpoints other than IPD. Thus, ELISA IgG data can only be used to bridge back to the demonstration of effectiveness of Prevnar 13 against IPD. The efficacy of Prevnar 13 against otitis media was also not assessed in a pre-licensure clinical endpoint study in children 6 through 17 years of age. Therefore, the proposed otitis media indication in this age group was not approved. Of note, as mentioned previously, with regards to PREA, the requirement to study the efficacy of Prevnar 13 against otitis media in children 6 through 16 years of age was waived due to the low incidence of otitis media in this age group.

In their Pharmacovigilance Plan, the Applicant proposes to carefully monitor for any unanticipated risks in ongoing clinical trials, surveillance systems of various countries, and postmarketing adverse reaction reports (i.e., routine pharmacovigilance). The review team concurs.

2. Clinical and Regulatory Background

Prevnar 13, a second generation pneumococcal conjugate vaccine (PCV), was licensed in the United States (US) on February 24, 2010 for the active immunization of children 6 weeks through 5 years of age for the prevention of invasive pneumococcal disease (IPD) caused by the 13 serotypes contained in the vaccine and for the prevention of otitis media caused by the seven original serotypes contained in Prevnar (1, 3, 5, 6A, 7F, and 19A). On December 20, 2011, Prevnar 13 was also approved in the US for the active

immunization of adults 50 years and older for the prevention of pneumonia and invasive disease caused by the 13 *S. pneumoniae* serotypes contained in the vaccine. In this submission, the Applicant proposes to expand the use of Prevnar 13 for the IPD and otitis media indications in children 6 through 17 years of age based on immunogenicity data from a single study conducted in the US and bridging back to infant IgG ELISA data from a primary Prevnar 13 infant pre-licensure study.

2.1 Disease or Health-Related Condition(s) Studied

Streptococcus pneumoniae is a major cause of morbidity and mortality in children and adults worldwide. Disease most commonly results when pneumococci colonized in the nasopharyngeal mucosa spread contiguously causing non-invasive disease such as otitis media, sinusitis and pneumonia.[1] IPD occurs when *S. pneumoniae* invades normally sterile body sites such as blood, cerebrospinal, pleural or peritoneal fluid. IPD disproportionally affects the very young, the elderly, certain ethnic groups, and those with underlying conditions.[2]

In 2010, the US Centers for Disease Control and Prevention's (CDC) Active Bacterial Core surveillance (ABCs) showed that IPD rates in US children and adolescents aged 5 through 17 years of age were the lowest among any other age group at 2.2 per 100,000 population.[3] The rates of IPD were also lowest in this pediatric age range (4.0 per 100,000) in 1998, prior to the introduction of Prevnar. In the US, individuals who are black or who are smokers are at higher risk of developing IPD compared to white and non-smokers, respectively. Other risk factors recognized by the US Advisory Committee on Immunization Practices (ACIP) include certain underlying medical conditions. The risk for IPD is greatest among persons who have congenital or acquired immunodeficiency, abnormal immune response, HIV infection, or functional or anatomic asplenia (i.e., sickle cell disease or congenital or surgical asplenia). Other underlying conditions associated with a higher risk of IPD include asthma, chronic cardiovascular (excluding hypertension), pulmonary, liver, or renal disease, diabetes mellitus, nephritic syndrome, leukemias, lymphomas, Hodgkin disease, generalized malignancy, solid organ transplantation, multiple myeloma, alcoholism, and cerebrospinal fluid leaks. Alaskan Native children and children among certain American Indian populations also have higher rates of IPD. Other risk factors include immunosuppressive drug use (including long-term systemic corticosteroids or radiation therapy) and a history of cochlear implant.[4]

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Two pneumococcal vaccines are currently available in the US. Pneumovax 23, the 23-valent pneumococcal polysaccharide vaccine (23vPS), was licensed in the US in 1983; it replaced a 14-valent formulation licensed in 1977. Pneumovax 23 is currently approved for routine use in persons ≥ 50 years of age and persons ≥ 2 years of age who are at increased risk of pneumococcal disease.[5] Each 0.5mL dose contains 25 µg of purified capsular polysaccharide from each of 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22, 23F, and 33F). These polysaccharide antigens are thought to be T-independent antigens that stimulate mature B-lymphocytes,

but not T-lymphocytes; they induce an immune response that is neither long-lasting nor anamnestic upon subsequent challenge. Pneumovax 23 is not approved for use in children < 2 years of age, because children in this age group generally have poor antibody responses to the vaccine.

Routine re-vaccination with Pneumovax 23 is not currently included in the package insert as an approved use of the vaccine.[6] The ACIP, which advises on the use of FDA licensed vaccines (outside of the FDA regulatory review process), provides recommendations regarding re-vaccination with Pneumovax 23. Revaccination of immunocompetent persons previously vaccinated with 23vPS is not routinely recommended by the ACIP; however, revaccination once, at least 5 years after receipt of the first dose, is recommended for persons ≥ 2 years of age who are at highest risk of serious pneumococcal infection.[5] According to ACIP, if prior vaccination status is unknown for high risk patients, then vaccination is indicated. Because data are not sufficient concerning the safety of 23vPS when administered ≥ 3 times, revaccination after a 2nd dose is not routinely recommended.

Prevnar was the first pneumococcal conjugate vaccine (PCV) licensed in the US on February 17, 2000 for use in children 6 weeks through 9 years of age. Although Prevnar is still licensed for use in the US, the manufacturer has stopped distributing the product in the US as of September 30, 2010. Conjugation of pneumococcal saccharides to the CRM_{197} protein creates saccharide-protein complexes which are thought to be capable of inducing a T-dependent immune response

The treatment of IPD consists of antibiotic therapy. Since the late 1970's, pneumococci have developed resistance to several classes of antibiotics, including beta-lactams, macrolides, tetracyclines, trimethoprim-sulfamethoxazile, glycopeptides, and fluoroquinolones. Until additional data is available to help clarify whether combination therapy or monotherapy is more appropriate for treating pneumococcal disease prior to availability of in vitro susceptibility testing, combination therapy using two antibiotics with different anti-pneumococcal mechanisms of action, is typically the treatment of choice. The choice of empiric antibiotic regimen depends on the local patterns of in vitro pneumococcal resistance. Once susceptibility results are available, therapy is typically reassessed and adjusted as necessary. The optimal duration of therapy also depends on several factors including the location of the primary infection, the patient's immune status, the presence of suppurative complications, and response to therapy.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no other US licensed pneumococcal conjugate vaccines.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Please refer to the Prevnar 13 package insert and/or the clinical review for the original Prevnar 13 Biologics License Application (BLA) or adult efficacy supplement for more information regarding previous human experience with Prevnar 13 in infants and children up through 5 years of age and in adults 50 years of age and older.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The original protocol for study 3011 was revised per CBER recommendations; revisions by the Applicant were limited, however, because enrollment had already been completed when CBER comments were received. Major revisions included (1) increasing the overall sample size to 300 subjects in each study group to enhance safety (groups 1-4) and immunogenicity (groups 3-4), (2) including OPA analysis of subjects in groups 3 and 4, (3) changing the primary endpoints and hypotheses, and (4) adding a historical control group. A summary of pre-submission amendments, communications and meetings that were important in attaining consensus on the study protocol and statistical analysis plan is provided below.

Relevant IND 11673 Amendments Received by CBER:

Aug 19, 2008:	Original protocol for study 3011 (Am 184 to IND 11673)
Oct 6, 2008:	Protocol Amendment #1 to Study 3011 (Am 189 to IND 11673)
Jan 7, 2009:	Protocol Amendment #2 to Study 3011 (Am 205 to IND 11673)
Jan 14, 2009:	SAP for Study 3011 (Am 207 to IND 11673)
Mar 3, 3009:	End of Phase 2 (EOP2) Meeting Responses (Am 214 to IND 11673)
Apr 22, 2009:	Study 3011 Comments (Am 221 to IND 11673)
Aug 13, 2009:	Protocol Amendment #3 to Study 3011 (Am 232 to IND 11673)
Apr 13, 2010:	Study 3011 Comments Regarding Groups 3 & 4 (Am 266 to IND 11673)
Dec 16, 2010:	Data from Exploratory Subset of Groups 3 & 4 and Proposed Analysis Plan (Am 295 to IND 11673)
May 17, 2011:	Responses to CBER Comments Dated Mar 17, 2011
Sep 8, 2011:	Responses to CBER comments dated Aug 11, 2011 and Proposal Concerning Groups 3 & 4
Oct 12, 2011:	Response to CBER comments dated Sep 16, 2011 regarding Wyeth's Sep 8 proposal (email communication)

Relevant Communications Issued by CBER:

Jan 22, 2009:	CBER comments regarding Am 189
Mar 20, 2009:	CBER comments regarding Am 214
Jun 4, 2009:	CBER comments regarding Am 221
May 27, 2010:	CBER comments regarding Am 266 (submitted 4/13/2010 to INDs 11673 & 13142). Telecon record available in BIRAMS under IND 13142.
Mar 17, 2011:	CBER comments regarding Am 295
Aug 11, 2011:	CBER comments regarding confirmatory cohort analysis for Groups 3 & 4
Sep 16, 2011:	CBER response to Proposal submitted by email on Sep 8, 2011

Relevant Meetings and Telecons between FDA and the Applicant:

Jan 28, 2009:	EOP2 face-to-face meeting
Jun 4, 2009:	Telecon
Sep 30, 2011:	Telecon – reached agreement on analysis plan for Groups 3 & 4

2.6 Other Relevant Background Information

In this submission, the applicant has submitted immunogenicity data (including IgG ELISA and microcolony OPA data) from study 3011 to support expanding the use of Prevnar 13 to children 6 through 17 years of age for the prevention of invasive pneumococcal disease. These data have, in part, been bridged to data from a population in which effectiveness has been demonstrated (i.e., Prevnar 13 in infants and toddlers). Because a new mcOPA assay was employed in study 3011 while the dOPA assay was used in the phase 3 Prevnar 13 pre-licensure studies in infants and toddlers (study 004 and 3005), bridging based on comparisons of functional antibody data as a primary endpoint was not possible [agreement between mcOPA and dOPA is low, thus comparisons between OPA antibody titers measured by different OPA assays are not to be attempted]. Therefore, a bridge was established based on IgG GMC data between children 5 through 9 years of age (an age group for which Prevnar was approved based on IgG data) to the corresponding post-dose 4 IgG GMC data in toddlers from study 6096A1-3005. The IgG ELISA assay used in study 3011 is identical to the IgG ELISA assay used in the Prevnar 13 pre-licensure studies (including study 3005). Study 6096A1-3005 was selected as the historical control because this study provided the largest dataset for Prevnar 13 recipients with regards to the 6 new serotypes contained in Prevnar 13. The Prevnar (control) group in study 6096A1-3005 was used for comparisons regarding the 7 original serotypes, as this provides a more direct link to efficacy. The serotype-specific mcOPA data from children 10 through 17 years of age in study 3011 was then compared the corresponding mcOPA data from children 5 through 9 years of age in study 3011.

Clinical Reviewer Note: CBER informed the Applicant on March 20, 2009 and June 4, 2009 that the immunogenicity data from study 3011 would not be considered to support the use of Prevnar 13 in 6 to 17 year olds for the prevention of disease endpoints other than IPD. This is because an immunologic bridge back to IgG ELISA antibody concentrations achieved by infants and toddlers one month after the 3rd or 4th dose of Prevnar 13 can only be used to infer effectiveness for the prevention of IPD.[7,8] The mechanism of protection against otitis media is not clearly understood, and there is no consensus regarding the serologic criteria for assessing effectiveness of second generation pneumococcal conjugate vaccines against otitis media. IgG antibody levels were not indicative of prevention of vaccine serotype otitis media in the prelicensure clinical trials with Prevnar (Clinical Review of STN 125324/0).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty or an unreasonable number of information requests.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch monitoring (BIMO) data audit inspections were issued for 4 clinical investigator sites (sites 3, 11, 18, and 26). No Form FDA 483 was issued for sites 3 and 26; however, at site 3, the BIMO investigator found 5 instances in which subjects received non-study vaccinations (flu and/or H1N1) on the same day as the study vaccine that were not listed on the non-study medications table (and consequently in the case report form and datasets). A Form FDA 483 was issued for sites 11 and 18. Items listed on the 483 for site 11 included two Group 3 subjects that did not previously receive Prevnar and 3 subjects that received non-study vaccines during the restricted window specified in protocol section 12.3. For site 18, items listed on the 483 included collection of blood samples that were below the protocol specification of (b)(4) mLs, not reporting to the sponsor that blood samples were not taken at visit 2 for 2 subjects, and 2 subjects who received non-study vaccinations during the restricted window specified in protocol section 12.3. The final classification of the inspection was voluntary action indicated for sites 11 and 18 and no action indicated for sites 3 and 26.

Clinical Reviewer Comment: With regards to the discrepancies noted between source documents and case report forms involving the documentation of non-study concomitant vaccinations, it was determined that the yield of any additional audits of study sites by the Applicant to verify the proportion of subjects that received concomitant vaccinations would likely be low. This is because the impact of concomitant vaccination was not a pre-specified study objective, and therefore subjects received varying concomitant vaccinations and/or combinations of concomitant vaccinations. In addition, the name and manufacturer of the concomitant vaccination was not always specified. Rather, study investigators may have noted the class of vaccine only (i.e., a flu vaccine). There was also inconsistent documentation of concomitant vaccinations in the electronic case report forms (see highlights from BIMO review in section 4.7). Thus, the potential yield of any further analyses by concomitant vaccination is likely to be very limited. In addition, based on preliminary subgroup analyses of immunogenicity results according to whether subjects received any non-study vaccine(s) concomitantly with Prevnar 13, it appeared that the immunogenicity responses for both IgG and OPA tended to be lower in subjects who received one or more non-study vaccinates concomitantly. Therefore, the review team agreed that any additional subjects who may have received non-study vaccines concomitantly with Prevnar 13 would have likely resulted in diminished overall immune responses among study 3011 participants and a trend toward the null hypothesis (i.e., failure to demonstrate non-inferiority compared to historical control). Please refer to the statistical review for additional information. The package insert will reflect that insufficient data were available to comment on any potential impact of concomitant administration of Prevnar 13 and routine pediatric vaccinations.

Clinical Reviewer Note: The Applicant clarified during the review of this Biologics License Application supplement (sBLA) that the original study protocol and subsequent protocol amendments allowed for concomitant administration of non-study vaccines with Prevnar 13 (i.e., at the same time and day that Prevnar 13 was administered). However, the protocol required a delay in the administration of Prevnar 13 in subjects who received any non-study vaccines up to 14 days (for non-live vaccines) or 28 days (for live

vaccines) prior to the day that the study vaccine was to be administered (study day 1). Subjects were also not permitted to receive non-study vaccines up through 6 days post-vaccination.

3.3 Financial Disclosures

On Form 3454, the sponsor certified that the following statement is correct:

"As the sponsor of the submitted studies, I certify that **I** have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Please refer to the original BLA submission (STN 125324/0), as the product formulation selected for use in persons 5 through 17 years of age is identical to the pediatric formulation which was approved in the original Prevnar 13 BLA.

4.2 Assay Validation

The ELISA assay used in this study was identical to the ELISA assay used in the original infant BLA, and the OPA assay used in this study was identical to the OPA assay used in the adult efficacy supplement. The pneumococcal ELISA and mcOPA assays were found to be appropriate for their intended use. Please refer to the serological immune response assay review, dated 9/4/2012, for more information.

4.3 Nonclinical Pharmacology/Toxicology

This submission contained no new nonclinical pharmacology/toxicology data. Please refer to the nonclinical (animal) pharmacology/toxicology review for the original BLA submission (STN 125324/0) or the adult efficacy supplement (STN 125324/262) for previously submitted data.

4.5 Statistical

The statistical reviewer concludes that the findings from study 3011 support the proposed expanded use of Prevnar 13 among 6 through 17 year old children for the invasive pneumococcal disease indication. The statistical reviewer also had the comments noted below. Please refer to the statistical review for more information.

- The data from study 3011 submitted to this sBLA included data from 5 year old children (in Group 3), for whom PCV13 is already approved. The study conclusions for study 3011 did not change for children in group 3 (5 through 9 year olds) regardless of the inclusion or exclusion of subjects 5 years of age.
- The comparisons between Group 3 in Study 3011 and the specified group in Study 3005 suggested higher IgG responses at post *Prevnar 13* vaccination in children 5 through 9 years of age when compared with the specified toddler group in Study 3005. It should be noted that when comparing the *pre-vaccination* IgG results in Group 3 of Study 3011 with the specified post-dose 4 IgG GMCs in Study 3005, the pre-specified non-inferiority criterion was met for 7 (3 of the original types and 4 of the additional types) of the 13 serotypes.
- Based on preliminary subgroup analyses of the immunogenicity results according to whether or not subjects received any non-study vaccination(s) concomitantly with the *Prevnar 13* vaccination, it appears that the immunogenicity responses (for both IgG and OPA antibodies) tended to be lower in subjects who received one or more non-study vaccinations concomitantly. The non-inferiority criterion was met in the subgroup where the subjects received *Prevnar 13* only. The sample size in the concomitant vaccination subgroup was small (between 30-40 subjects) and therefore resulted in insufficient statistical power to make non-inferiority comparisons. It should be noted that the data collected in the study might be incomplete due to different data collection procedures across the sites. Therefore, based on results provided in this submission, it is premature to draw any conclusion with regard to the impact or interference of other vaccine(s) when administered concomitantly with *Prevnar 13*.

4.6 Pharmacovigilance

The OBE postmarketing safety reviewer concurs with continued routine safety surveillance. OBE does not request a monthly listing of non-15 day AEs for children 6 through 17 years of age. To date, no safety signals have been identified that would justify a postmarketing requirement.

4.7 Bioresearch Monitoring (BIMO)

The BIMO reviewer concludes that the BIMO inspections did not reveal problems that impact the data submitted in the application. Four clinical investigator sites were inspected (sites 03, 11, 18, and 26). Significant inspection findings included the following: Nine instances of subjects receiving non-study vaccinations on the same day as the study vaccine (or within the restricted window identified in Protocol section 12.3) that were not listed on the “Non-Study Medications Table” submitted with the sBLA. It was noted that the electronic case report form (eCRF) had an optional field for other medications and did not have a field to record concomitant vaccinations. Not all sites recorded concomitant vaccinations in the same location on the eCRF or reported subjects who received a non-study vaccination as a protocol deviation to the sponsor. The sponsor noted that there were a few different versions of the CRF at the clinical sites. The use of different eCRFs resulted in inconsistencies in documenting and reporting concomitant vaccinations. Please refer to the BIMO review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on the single study submitted to this sBLA (study 6096A1-3011). An integrated summary of safety and efficacy is not presented, because this submission consists of one study.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following modules of the sBLA were reviewed:

m1.6	Meetings
m1.11.3	Efficacy Information Amendments
m1.14	Labeling
m2.5	Clinical Overview
m2.7	Clinical Summary
m5	Clinical Study Reports

A detailed list of information reviewed in the sBLA is below by amendment number:

STN 125324/767.1, Amendment 1: Submitted 7/18/2012

- m1.16 Risk Management Plans

STN 125324/767.2, Amendment 2: Submitted 8/6/2012

- m1.11.3 Efficacy Information Amendment: Response to July 13, 2012 CBER comments
- m5.3.5.1.3 CSR-76155 Addendum (Study 3011) from December 2010, "Final Safety Addendum for Groups 1 and 2, Cohort 2…"

STN 125324/767.3, Amendment 3: Submitted 9/7/2012

- m1.11.3 Efficacy Information Amendment: Response to 8/13/2012 CBER Comments, Immunogenicity Subgroup Analyses

STN 125324/767.4, Amendment 4: Submitted 10/1/2012

- m1.11.3 Efficacy Information Amendment: Pooled analyses of AE data for cohorts 1 and 2. Datasets submitted to m5.3.5.1

5.3 Table of Studies/Clinical Trials

The clinical section of the application contains a single study report in persons 5 through 17 years of age.

Table 1. Clinical Study Included in the PCV13 BLA Supplement in 5 through 17 Yr Olds

Study No.	Description	Schedule (months)	Control	Concomitant Vaccines	Number Vaccinated (as randomized)	
					Group 3: ≥ 5 to < 10 yrs old	Group 4: ≥ 10 to < 18 yrs old
6096A1-3011 Grps 3 and 4[a] (USA)	Safety and immunogenicity of 1 dose of PCV13 in persons 5 thru 17 years of age	PCV13, Single Dose	None	Permitted, but not required	294	298

[a] Subjects in group 3 had previously received at least 1 dose of PCV7 and subjects in group 4 had never received any pneumococcal vaccine.

5.5 Literature Reviewed

1 World Health Organization. 23-valent pneumococcal polysaccharide vaccine WHO position paper. Weekly Epidemiological record. 2008; 83(42):373-384.

2 Singleton RJ, Butler JC, Bulkow LR et al. Invasive pneumococcal disease epidemiology and effectiveness of 23-valent pneumococcal polysaccharide vaccine in Alaska Native adults. Vaccine. 2007; 25:2288-2295.

3 2010 ABCs data: Active Bacterial Core Surveillance (ABCs) Report: *Streptococcus pneumoniae*, 2010, Emerging Infections Program Network. Available at: http://www. cdc.gov/ abcs/reports-findings/survreports/spneu10.pdf. Accessed 12/14/2012.

4 MMWR Recommendations and Reports. Prevention of Pneumococcal Disease Among Infants and Children – Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). 12/10/2010. vol 59 No. RR-11.

5 Nuorti JP, Whitney CG. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR. 2010;59(34):1102-1106.

6 Merck & Co., Inc. Pneumovax 23 Package Insert. Revised 2011.

7 Feavers I, et al. Meeting Report: Challenges in the Evaluation and Licensing of New Pneumococcal Vaccines, 7-8 July 2008, Ottawa, Canada. Vaccine 2009;27:3681-3688.

8 Feavers I, Frasch D, Jones C, et al. Annex 2: Recommendations for the production and control of pneumococcal conjugate vaccines. WHO Technical Report Series. 2005;927:64-98.

9 Merikangas KR, He J, Burstein M et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication – Adolescent Supplement (NCS-A). Journal of the American Academy of Child and Adolescent Psychiatry. 2010;49(10):980-989.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Clinical Study Protocol # 6096A1-3011
Clinical trials.gov registry identifier: NCT00761631

Protocol Title: An open-label trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy children aged 15 months to 17 years in the United States. Study dates (groups 3&4): 11/18/2008 – 8/10/2010. Serology date (groups 3&4): 11/4/2011.

Clinical Reviewer Note:

- The protocol for study 3011 was amended in August 2009 (Amendment 3) to increase the sample size to 1200 subjects (300 subjects in each group). Originally, the study was designed to include 125 subjects in group 1, 182 subjects in group 2, and 100 subjects in each of groups 3 and 4. Additional subjects were enrolled to enhance the precision of the immunogenicity results (groups 3 and 4) and provide additional safety data (groups 1-4). Subjects enrolled into groups 1 and 2 prior to amendment 2 were classified as cohort 1. Additional subjects enrolled into groups 1 and 2 as part of amendment 3 were classified as cohort 2 and were only evaluated for safety.
- Data for Groups 1 and 2 (children 15 months through 4 years of age): Data from study 3011 were submitted in two separate efficacy supplements. Data from the first cohort for children up through 4 years of age (Groups 1 and 2) through one month post-vaccination were submitted to the original Prevnar 13 BLA in support of a supplemental PCV13 vaccination in children 15 months through 5 years of age previously immunized with at least 3 doses of Prevnar. Data from cohort 2 of groups 1 and 2 and 6-month safety data for all (cohorts 1 and 2) children in groups 1 and 2 were to be submitted in a subsequent study report along with safety and immunogenicity data for 5 through 17 years olds (groups 3 and 4).
- Safety and immunogenicity data for children 6 through 17 years of age were considered a deferred postmarketing requirement under PREA and were submitted to this efficacy supplement to support expanding the use of Prevnar 13 to children in this age group. The safety data for cohort 2 children in groups 1 and 2 (i.e., 15 months through 4 years of age) and the 6-month post-vaccination follow-up safety data for cohort 1 and 2 subjects in Groups 1 and 2 were also submitted to this supplement.
- The data for cohort 2 subjects are summarized as pooled safety data.

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective for Groups 3 and 4 was to assess the pneumococcal immune responses induced by PCV13 when measured 1 month after the last scheduled study vaccination. The exploratory objective was to assess the level of opsonophagocytic activity (OPA) induced by PCV13 measured 1 month after the last scheduled dose of PCV13. The safety objective was to evaluate the acceptability of the safety profile of PCV13 as measured by the incidence of local reactions, systemic events and adverse events (AEs).

Clinical Reviewer Note: Please see section 6.1.9 for hypothesis testing details.

6.1.2 Design Overview

This was an open-label, phase 2/3, nested-exploratory, non-randomized, multicenter study in which subjects were enrolled into 1 of 4 groups based on age at enrollment (see Table 2 below). Data from study groups 1 and 2, which included children ≥ 15 months to < 5 years of age, were included in the original Biologics License Application (BLA) to support a supplemental dose of Prevnar 13 among children who completed the 4-dose Prevnar (PCV7) series and are described in the Prevnar 13 package insert. The evaluation of Prevnar 13 safety and immunogenicity in groups 3 and 4, which included subjects ≥ 5 to < 18 years of age, is considered to be the "age-expansion" study and is a deferred postmarketing requirement under the Pediatric Research Equity Act (PREA). Immunogenicity data from the first 100 subjects enrolled into each of groups 3 and 4 (the exploratory cohort) were used to establish the primary endpoint and criteria for testing in the confirmatory cohort (the next 200 subjects enrolled in each of groups 3 and 4). Immunogenicity data from group 3 subjects (5 through 9 years of age) were compared to the immunogenicity data from a historical control group (post-dose 4 data from infant study 6096A1-3005). Immunogenicity data from group 4 subjects (10 through 17 years of age) were compared to the immunogenicity data from group 3.

Table 2. Study Design

Population	Vaccine	Dosing Schedule	Duration of Subject Participation
Group 1: ≥ 15 months to < 2 yrs of age with ≥ 3 prior PCV7 doses	PCV13	2 doses, ≥ 56 days apart	8 months
Group 2: ≥ 2 to < 5 yrs of age with ≥ 3 prior PCV7 doses	PCV13	1 dose	6 months
Group 3: ≥ 5 to < 10 yrs of age with ≥ 1 prior PCV7 dose	PCV13	1 dose	6 months
Group 4: ≥ 10 to < 18 yrs of age who never received a pneumococcal vaccine	PCV13	1 dose	6 months

Clinical Reviewer Note:
Because a clinical endpoint study was not feasible in this age group due to the low incidence of disease, evaluation of effectiveness in this age group is limited to immunogenicity data. Weaknesses in the study design used for this trial include the lack of blinding and randomization, and the use of a historical control. Although the use of IgG GMCs as the primary endpoint for study group 3 (5 thru 9 yr olds) was acceptable (given the approval of Prevnar 13 for children up through 9 years of age based on IgG data), the use of OPA antibody titers as the primary endpoint would have been a more robust endpoint. The measurement of IgG antibodies includes some amount of non-functional antibodies; in addition, there does not appear to be correlation between OPA

and IgG measurements of serum antibodies. The study also did not enroll children at increased risk of pneumococcal disease, who are the primary target population for vaccination in this age group. For details regarding the regulatory history for this study protocol and statistical analysis plan, please refer to section 2.5.

6.1.3 Population

Inclusion criteria:
1. Male or female between ≥ 5 years and < 18 years of age at the time of enrollment.
2. Child available during study period and parent/legal guardian reachable by phone.
3. Child in good health by medical history, physical exam, and judgment of investigator.
4. The parent/legal guardian able and willing to comply with all study procedures.
5. Group 3 only: written documentation endorsed by a health professional showing previous vaccination with at least 1 dose of Prevnar in children ≥ 5 to < 10 years of age. The last dose of Prevnar must have been received at least 56 days before study entry.
6. Group 4 only: negative urine pregnancy test for menstruating female subjects.
7. Group 4 only: all female and male subjects biologically capable of having children agreed to abstinence or committed to the use of a reliable method of hormonal and/or non-hormonal contraception for 3 months after vaccination.

Exclusion criteria:
1. Previous anaphylactic reaction to any vaccine or vaccine-related component.
2. Contraindication to vaccination with a pneumococcal conjugate vaccine.
3. Bleeding diathesis or condition associated with prolonged bleeding time that would have contraindicated intramuscular injection.
4. History of culture-proven invasive disease caused by *S. pneumoniae*.
5. Major known congenital malformation or serious chronic disorder.
6. Significant neurological disorder or history of seizure (excluding simple febrile seizure), or significant stable or evolving disorder such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorder.
7. Receipt of blood products or gamma-globulin.
8. Known or suspected immune deficiency or suppression.
9. Participation in another investigational or interventional trial. Participation in purely observational studies was acceptable.
10. Child was a direct descendant (child or grandchild) of site study personnel.
11. The subject had been previously vaccinated with 23-valent pneumococcal polysaccharide.
12. Group 4 only: children aged ≥10 years to <18 years who had previously been vaccinated with Prevnar or any other pneumococcal vaccine.
13. Group 4 only: pregnant or breastfeeding adolescent females.

Temporary Delay Criteria:
Subjects with the following temporary or self-limiting conditions could be vaccinated once the condition(s) resolved:
1. Current febrile illness (temp ≥ 38.0°C) or other acute illness ≤ 48 hours before study vaccination.

2. Receipt of any non-live vaccine within the previous 14 days or live vaccine within the previous 28 days. [Such vaccines may have been given at least 7 days after study vaccination.]
3. Subject is < 5 days into a course of antibiotic therapy for other acute illness.
4. Lack of written documentation by health professional showing previous PCV7 vaccination for subjects < 10 years of age in groups 1, 2, and 3.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Prevnar 13: Each 0.5ml dose contains 2.2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4ug saccharide for 6B individually conjugated to CRM197. The total concentration of CRM_{197} is 34ug. The final formulation contains 5mM succinate buffer ----------(b)(4)---------- with 0.125 mg aluminum as $AlPO_4$ and 0.02% polysorbate 80. The vaccine is formulated as a liquid and appears as a homogeneous, white suspension after shaking. The vaccine is provided in pre-filled single-dose syringes without preservatives. Route: a single dose was administered by intramuscular injection in left arm or leg. Lot number for vaccination: 7-5095-005A.

Permitted concomitant medications/vaccinations included:

- Routine pediatric vaccinations may have been given at the same time as study vaccination according to local or national recommendations. The name and date of concomitant vaccine administration were captured in the CRF.
- A local anesthetic at the site of the blood draw;
- Topical and inhaled corticosteroids; and
- Antipyretic medications to treat or prevent vaccine-related symptoms.

Clinical Reviewer Note:
Although study 3011 did not include a pre-specified objective to evaluate for potential interference when Prevnar 13 is administered concomitantly with routine pediatric vaccines, the study protocol permitted routine pediatric non-study vaccines to be administered concomitantly with the study vaccine or 7 days *after* the study vaccine according to local or national recommendations. Non-live vaccine could not be given within the *prior* 14 days of study vaccine and live vaccines could not be given within 28 days prior to the study vaccine (see temporary delay criteria in section 6.1.3). Non-study vaccines were also not permitted if administered within 6 days *after* the study vaccination. Documentation of non-study vaccinations were made on optional CRF pages to be completed only if the subject either (1) received a non-study vaccine 56 days prior to or at visit 1 or (2) received a non-study vaccine after visit 1. The limb which received the non-study vaccination was not recorded in the CRF. CBER requested post-hoc subgroup analyses by concomitant vaccination status (i.e., those who received PCV13 concomitantly with other non-study vaccines and those who received PCV13 alone) to evaluate for any potential impact of concomitant vaccination on immune response and safety.

6.1.5 Directions for Use

Directions for use are specified in the Prevnar 13 package insert.

6.1.6 Sites and Centers

Subjects in groups 3 and 4 were enrolled in the study from 29 sites in the United States.

6.1.7 Surveillance/Monitoring

Safety Monitoring:

1. Immediate reactions: 30 minutes observation
2. Solicited adverse events (AEs): local and systemic events monitored by parent(s)/legal guardian(s) and recorded in an e-diary on days 1-7 after vaccination (day of vaccination = day 1). For events present on day 7, the e-diary prompted the parent(s)/legal guardian(s) to update the status of the event until an end date.
    a. Local adverse reactions: erythema, induration, and tenderness at administration site of pneumococcal vaccine
    Erythema and induration grading scale: 0: absent = none (0 caliper units); 1: mild = 0.5 - 2.4cm (1-4 caliper units); 2: moderate = 2.5 - 7.0cm (5-14 caliper units); 3: severe = > 7.0cm (> 14 caliper units). If a reaction is > 7.0cm, the parent/legal guardian was to contact study personnel for evaluation at an additional study visit. Measurements were of the largest diameter and were rounded up to the nearest whole number. One caliper unit = 0.5 cm.
    Tenderness grading scale: not present, present, present and interferes with limb movement.
    b. Systemic AE: decreased appetite, irritability, increased sleep, decreased sleep, hives (urticaria), fever (core (rectal) temperature > 38.0^{o}C), and use of antipyretic medication. Temperature was measured daily at bedtime and any time when fever was suspected during days 1-7 post-vaccination using an age appropriate method. Parents were instructed to record the highest temperature daily, and were given instructions how to use the provided thermometer to perform oral or rectal measurements as appropriate. For groups 3 and 4, the most commonly used route would have been oral. If fever developed, temperature was measured daily until the subject was afebrile for 24 hours.
    Temperature grading scale: absent: < 38.0^{o}C; mild: ≥ 38.0 to ≤ 39.0^{o}C; moderate: > 39.0 to ≤ 40.0^{o}C; severe: > 40.0^{o}C
    Rash categorization: Parents were instructed to contact study staff if a rash is suspected. Study staff would set up an additional study site visit if they believed the child had hives.
    No grading scale for other solicited systemic AE.
3. Unsolicited AEs and serious AEs (SAEs) were collected throughout the study period.
4. A telephone call was planned 6-months after vaccination to record newly diagnosed chronic medical conditions, hospitalizations, and SAEs that occurred since the last study visit.

Clinical Reviewer Note: Prevnar 13 was to be administered into the left arm or leg, and the site of administration was recorded in the CRF. Of note, the site of administration of non-study concomitant vaccinations was not recorded in the CRF. The applicant states that parent instructions for recording solicited local reactions were not limb specific, so that if the vaccine was given in the incorrect limb, the eDiary screen was to be the same to capture reactogenicity from the site of Prevnar 13 administration. Most subjects were

noted to receive Prevnar 13 in the left arm or leg (left arm – 543; left leg – 37; right arm – 11; right leg – 1).

Immunogenicity Monitoring:

- Blood samples were to be obtained before vaccination on day 1 and 1 month after vaccination.
- Immunogenicity assays (including pneumococcal IgG ELISA and OPA assays) were performed by Early Phase Programs – Clinical Testing and Assay Development (EPP-CTAP) Wyeth.
  - The ELISA assay employed 2 absorbents: a C-polysaccharide-containing ----------(b)(4)---- plus serotype 22F capsular polysaccharide. Serotype-specific ELISA LLOQs ranged from ----------(b)(4)----------. Serotype-specific LODs ranged from ----------(b)(4)----------.
  - The microcolony OPA assay was used to determine serum OPA antibody titers. Serotype-specific OPA LLOQs are listed below. The LOD was established as the lowest titer possible, or (b)(4) for all serotypes.

Serotype 1: (b)(4)	Serotype 9V: (b)(4)
Serotype 3: (b)(4)	Serotype 14: (b)(4)
Serotype 4: (b)(4)	Serotype 18C: (b)(4)
Serotype 5: (b)(4)	Serotype 19A: (b)(4)
Serotype 6A: (b)(4)	Serotype 19F: (b)(4)
Serotype 6B: (b)(4)	Serotype 23F: (b)(4)
Serotype 7F: (b)(4)	

  - IgG concentrations and OPA antibody titers below the LLOQ were set to 0.5 * LOD.

<u>Clinical Reviewer Note</u>:
CBER requested a post-hoc sensitivity analysis in which GMTs were recalculated using actual OPA antibody titers, 0.5*LLOQ, 0.75*LLOQ, 0.80*LLOQ, and 1.0*LLOQ for those titers that fell below the LLOQ. A comparison of OPA antibody titers categorized as the primary endpoint for the group 4 confirmatory cohort was repeated using these recalculated OPA antibody GMTs (Data not shown – Tables 9-17 to 9-21 in clinical study report). CBER also requested data regarding the proportion of subjects in each study group that achieved an OPA antibody titer ≥ LLOQ for the mcOPA assay.

Table 3. Study Flowchart for Group 3: Aged ≥ 5 to < 10 Years

Visit Number	**1**	**2**	**3**
Visit ID	**Grp 3, Visit 1**	**Grp 3, Visit 2**	**Grp 3, Visit 3**
Study Interval	**Vaccination 1**	**Post-vaccination Follow-Up**	**6 Month Telephone Follow-Up**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**165 to 210 Days After Visit 1**
Informed consent	X		
Review inclusion and exclusion criteria	X		
Confirm continued eligibility		X	
Medial history, demography and physical examination	X		
Temperature (measured as appropriate for age)	X		
Obtain blood sample	X	X	
PCV13 administration	X		
30 min observation	X		
AE collection	X	X	X
Provide thermometer, e-diary, and caliper	X		
Record solicited AEs using e-diary	Days 1 to 7		
Review e-diary		X	
Collect e-diary		X	

Table 4. Study Flowchart for Group 4: Aged ≥ 10 to < 18 Years

Visit Number	**1**	**2**	**3**
Visit ID	**Grp 4, Visit 1**	**Grp 4, Visit 2**	**Grp 4, Visit 3**
Study Interval	**Vaccination 1**	**Post-vaccination Follow-Up**	**6 Month Telephone Follow-Up**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**165 to 210 Days After Visit 1**
Informed consent	X		
Review inclusion and exclusion criteria	X		
Urine pregnancy tests for female subjects who are menstruating	X		
Confirm continued eligibility		X	
Medial history, demography and physical examination	X		
Temperature (measured as appropriate for age)	X		
Obtain blood sample	X	X	
PCV13 administration	X		
30 min observation	X		
AE collection	X	X	X
Provide thermometer, e-diary, and caliper	X		
Record solicited AEs using e-diary	Days 1 to 7		
Review e-diary		X	
Collect e-diary		X	

6.1.8 Endpoints and Criteria for Study Success

For Group 3, the primary endpoint was the IgG GMCs at 1 month post-vaccination. For Group 4, the primary endpoint was the OPA antibody GMTs at 1 month post-vaccination. The secondary endpoint for Group 4 was the IgG GMCs at 1 month post-vaccination.

6.1.9 Statistical Considerations & Statistical Analysis Plan

- This was an open-label study and subject allocation to age groups was based on the subject's age at enrollment.
- Two immunogenicity analysis populations were defined. The criteria for inclusion in each analysis population are described below.
    - Evaluable immunogenicity population (primary analysis population): being eligible, enrolled, in the protocol specified age range for either group 3 or 4, received the required study vaccination, had at least 1 valid and determinate assay result before or after vaccination contributing to the

planned analysis, had blood drawn before or after vaccination within the required time frame (27 to 56 days post-vaccination), and had no other major protocol violations.
    - All-available immunogenicity population: having at least 1 valid and determinate assay result.
- Primary hypotheses:
  1. To demonstrate that the IgG GMC for each of the 7 common pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) one month after vaccination with Prevnar 13 in subjects 5 through 9 years of age in study 6096A1-3011 is non-inferior to the corresponding IgG GMC one month after the fourth dose of Prevnar (given to toddlers at 12-15 months of age) in the phase 3 pre-licensure PCV13 study numbered 6096A1-3005.
     Criterion for non-inferiority: lower limit of the 2-sided 95% CI for the ratio of the GMCs (group 3 confirmatory cohort / study 3005 PCV7 recipients) > 0.5.
  2. To demonstrate that the IgG GMC for each of the 6 additional pneumococcal serotypes included in Prevnar 13 (1, 3, 5, 6A, 7F, and 19A) one month after vaccination with Prevnar 13 in subjects 5 through 9 years of age in study 6096A1-3011 is non-inferior to the corresponding IgG GMC one month after the fourth dose of Prevnar 13 (given to toddlers at 12-15 months of age) in the phase 3 pre-licensure PCV13 study numbered 6096A1-3005.
     Criterion for non-inferiority: lower limit of the 2-sided 95% CI for the ratio of the GMCs (group 3 confirmatory cohort / study 3005 PCV13 recipients) > 0.5.
  3. To demonstrate that the OPA antibody GMTs for each of the 13 pneumococcal serotypes included in Prevnar 13 one month after vaccination with Prevnar 13 in subjects 10 thru 17 years of age in study 6096A1-3011 are non-inferior to the corresponding OPA antibody GMTs one month after vaccination with Prevnar 13 in subjects 5 through 9 years of age in study 6096A1-3011.
     Criterion for non-inferiority: lower limit of the 2-sided 95% CI for the ratio of the OPA antibody GMTs (group 4 confirmatory cohort / group 3 confirmatory cohort) > 0.5.
- Safety analysis population: included all subjects who received one dose of PCV13. Safety was descriptively summarized.
- Originally, the study was sized to allow estimation of the proportion of responders to within ± 5% precision in each age group. Per a request from the FDA, the sample size was increased to 300 subjects per group to enhance precision of the immunogenicity results and provide additional safety data for PCV13 in older children.

6.1.10 Study Population and Disposition

All of the 598 subjects who were consented were enrolled and randomized, and the majority of enrolled subjects were vaccinated (Table 5). A higher proportion of subjects withdrew in group 3 (7.4%) compared to group 4 (1.7%).

Table 5. Study 6096A1-3011. Summary of Subject Disposition

	Group 3e (≥ 5 to < 10 yrs) N=100		**Group 3c (≥ 5 to < 10 yrs) N=199**		**Group 3e+3c (≥ 5 to < 10 yrs) N=299**		**Group 4e (≥ 10 to < 18 yrs) N=100**		**Group 4c (≥ 10 to < 18 yrs) N=199**		**Group 4e+4c (≥ 10 to < 18 yrs) N=299**	
	n	%	n	%	n	%	n	%	n	%	n	%
Enrolled	100	100.0	199	100.0	299	100.0	100	100.0	199	100.0	299	100.0
Vaccinated												
Dose 1	98	98.0	196	98.5	294	98.3	100	100.0	198	99.5	298	99.7
Completed	93	93.0	184	92.5	277	92.6	98	98.0	196	98.5	294	98.3
Withdrawn	7	7.0	15	7.5	22	7.4	2	2.0	3	1.5	5	1.7
Reason for withdrawal												
Failed to return	1	1.0	4	2.0	5	1.7	1	1.0	1	0.5	2	0.7
Lost to follow-up	0	0.0	6	3.0	6	2.0	1	1.0	0	0.0	1	0.3
Protocol violation[a]	2	2.0	3	1.5	5	1.7	0	0.0	1	0.5	1	0.3
Parent/legal guardian request	4	4.0	1	0.5	5	1.7	0	0.0	0	0.0	0	0.0
Other[b]	0	0.0	1	0.5	1	0.3	0	0.0	1	0.5	1	0.3

[a] In group 3, 2 subjects received no prior dose of PCV7 and they received a prior dose of investigational PCV13 in another clinical trial, thus they were not eligible to continue; 2 subjects never received a prior dose of PCV7 and were thus entered into the study in error (both of the latter 2 subjects completed the visit 3 follow-up); and 1 subject had received PPSV23. In group 4, 1 subject had a history of 2 prior doses of PCV7 and was randomized in error.
[b] One group 3 subject was "uncooperative" and one group 4 subject was "unable to withdraw blood".
Source: STN 125324/767.0, m5.3.5.1.3, Clinical Study Report (CSR), Tables 14-2 and 14-3, p 143. STN 125324/767.0, m5.3.5.1.16, Discontinued Patients, p 1-3.

6.1.10.1 Populations Enrolled/Analyzed

Of the 598 subjects enrolled, 593 were eligible for inclusion in the all-available (or intention-to-treat) immunogenicity population and 558 were eligible for inclusion in the evaluable (or pre-protocol) population. Please see section 6.1.9 for definitions of the analysis populations. Unless otherwise specified, results from the all-available population were similar to the results of the evaluable population, which was the primary analysis population. Please see section 6.1.10.1.3 for details regarding subject disposition.

6.1.10.1.1 Demographics

The overall safety population included a higher proportion of males than females in group 4. In addition, a higher proportion of white subjects and a lower proportion of black subjects were included in group 4 compared to group 3 (Table 6). Over 90% of subjects were characterized as non-Hispanic and non-Latino. The demographics for the

evaluable immunogenicity population were similar (Data not shown – Table 8-9 of the clinical study report).

In the exploratory and confirmatory cohorts, some differences were noted (Data not shown, Tables 14-22 and 14-23 of clinical study report). In group 3, the exploratory subset included a higher proportion of males (55.1%) while the confirmatory cohort included a higher proportion of females (56.1%). In addition, the confirmatory cohorts of groups 3 and 4 included a lower proportion of white subjects compared to the exploratory subset [(3c: 62.2% vs 3e: 77.6%); (4c: 74.2% vs 4e: 86.0%)] and a higher proportion of black subjects compared to the exploratory subset [(3c: 30.1% vs 3e: 18.4%); (4c: 20.7% vs 4e: 11.0%)].

Table 6. Demographic Characteristics for All Subjects

	Group 3e+3c (≥ 5 to < 10 yrs) N=294		**Group 4e+4c (≥ 10 to < 18 yrs) N=298**		**Total N=592**	
	n	%	n	%	n	%
Sex						
Male	140	47.6	163	54.7	303	51.2
Female	154	52.4	135	45.3	289	48.8
Race						
White	198	67.3	233	78.2	431	72.8
Black	77	26.2	52	17.4	129	21.8
Other	13	4.4	6	2.0	19	3.2
Asian	5	1.7	4	1.3	9	1.5
American Indian or Native Alaskan	1	0.3	3	1.0	4	0.7
Ethnicity						
Non-Hispanic and Non-Latino	269	91.5	272	91.3	541	91.4
Hispanic or Latino	25	8.5	26	8.7	51	8.6
Enrolment Age (yrs)						
Mean (SD)	7.4 (1.3)		13.7 (2.1)		10.3 (3.6)	
Median	7.5		13.6		10.1	
Min, Max	5.0, 10.0		10.0, 18.0		5.0, 18.0	
Weight at enrollment (kg)						
n	291		296		587	
Mean (SD)	28.3 (8.8)		58.2 (18.4)		43.4 (20.8)	
Median	26.4		55.8		39.1	
Min, Max	15.2, 66.8		23.1, 130.0		15.2, 130.0	

Source: STN 125324/767.0, m5.3.5.1.3, CSR, Table 14-21, p 168.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population (Data not shown, Table 14-29 in clinical study report)
The percentage of subjects with a history of psychiatric disorders was higher in group 4 (21.4%) than in group 3 (12.0%), and the most common individual diagnosis under psychiatric disorders was attention deficit/hyperactivity disorder (ADHD) (9.4% in group 3 and 16.4% in group 4). Other noted differences in system organ class terms included infections and infestations (33.1% in group 3, 23.7% in group 4) and metabolism and nutrition disorders (3% in group 3, 7.4% in group 4).

Differences in individual diagnoses between group 3 and 4 included depression (0.7% in group 3, 3.0% in group 4), obesity (1.3% in group 3, 4.0% in group 4), seasonal allergy (4.3% in group 3, 9.7% in group 4), and several terms under the infections and infestations system organ class (i.e., otitis media, pneumonia, upper respiratory tract infection, ear infection, and bronchiolitis).

Clinical Reviewer Note: The prevalence rates of mental disorders observed in this study are consistent with rates published in the scientific literature. According to the National Comorbidity Survey Adolescent Supplement, which is a nationally representative face-to-face survey of 10,123 adolescents aged 13 to 18 years in the continental US, the lifetime prevalence estimates of mental disorders were 14.3% for any mood disorder, 31.9% for any anxiety disorder, and 19.6% for any behavioral disorder (including ADHD).[9] Some of the differences in medical history noted above could be related to higher rates of diagnosis in 10 through 17 year old subjects compared to 5 through 9 year old subjects. It is noted that 17.4% (52/299) of enrolled subjects in both groups 3e+3c and 4e+4c reported a medical history of asthma.

The numbers of subjects who received Prevnar prior to the study are described below. A majority (83.6%) of group 3 subjects received 3 or 4 prior doses of Prevnar. The rates of prior Prevnar vaccination were similar between the exploratory and confirmatory cohorts of group 3. No subject in group 4 received a prior dose of Prevnar.

Table 7. Number of Prevnar Doses Received Before Study Enrollment, Group 3.

# Prior Prevnar Doses	Group 3e + 3c (≥ 5 to < 10 yrs) N=299	
	n	%
0	5	1.7
1	15	5.0
2	28	9.4
3	87	29.1
4	163	54.5
5	1	0.3

Source: STN 125324/767.0, m5.3.5.1.3, CSR, Table 14-41, p 207.

Non-Study Vaccinations During the Study Period (Data not shown, Table 14-38 to 14-40 in clinical study report):
Among all study subjects (confirmatory and exploratory cohorts), a total of 84 (28.1%) of group 3 subjects and 101 (33.8%) of group 4 subjects received a nonstudy vaccine during the study. Nonstudy vaccines were more commonly received by subjects in the confirmatory cohort compared to the exploratory subset. The most commonly received non-study vaccine was influenza vaccines. Among group 3 subjects, 9% (9/100) in group 3e and 33.7% (67/199) in group 3c received an influenza vaccine. In group 4 subjects, 13% (13/100) in group 4e and 33.2% (66/199) in group 4c received an influenza vaccine.

Non-Study Vaccinations From 28 Days Prior to 6 Days After PCV13 Administration in the Confirmatory Cohort (Data not shown, table 1 in STN 125324/767.3, m1.11.3):

- A live vaccine was administered to 1 subject (Grp 4, varicella) from 28 days up through 1 day prior to study vaccination.
- Non-live vaccines were administered to 3 subjects (2 Grp 3 subject, 1 Grp 4 subject) from 14 days up through 1 day prior to study vaccination. This included influenza vaccine in group 3 and influenza, meningococcal, pertussis, and HPV vaccines in group 4.
- Live and non-live non-study concomitant vaccines were administered to 82 subjects (41 Grp 3 subjects and 41 Grp 4 subjects) on study day 1, the day of study vaccination.
- No non-study vaccines were administered on days 2 through 6 post-vaccination.

6.1.10.1.3 Subject Disposition
Subject disposition is described for the confirmatory cohorts in Table 8 below.

Within Group 3e+3c, 295 (98.7%) subjects were included in the all-available immunogenicity population and 272 (91%) subjects were included in the evaluable immunogenicity population. Four subjects were excluded from the 3e+3c all-available population, and 27 subjects were excluded from the 3e+3c evaluable population (Data not shown, Table 9-1 in CSR). Within Group 4e+4c, 298 (99.7%) were included in the all-available population, and 286 (95.7%) were included in the evaluable population. One subject was excluded from the 4e+4c all-available population, and 13 subjects were excluded from the 4e+4c evaluable population (Data not shown, Table 9-1 in CSR).

Table 8. All-Available and Evaluable Immunogenicity Populations (Confirmatory Cohorts)

	Group 3c (≥ 5 to < 10 yrs)		**Group 4c (≥ 10 to < 18 yrs)**	
	n	%	n	%
Enrolled	199	100.0	199	100.0
All-available Immunogenicity Population	196	98.5	198	99.5
Excluded from all-available population, because there was no assay result for any serotypes before or after vaccination	3	1.5	1	0.5
Evaluable Immunogenicity Population	182	91.5	190	95.5
Excluded from evaluable population[a]	17	8.5	9	4.5
No assay result for any serotype before or after vaccination	13	6.5	3	1.5
Not in all-available population	3	1.5	1	0.5
Group 3 subject had no prior PCV7 doses, was withdrawn b/c received PCV13 in another trial	2	1.0	0	0.0
Not eligible for study	1	0.5	3	1.5
Received prior dose of PCV7 < 56 days prior to visit 1	1	0.5	0	0.0
Blood draw < day 1 before 1st vaccination	0	0.0	3	1.5
Receipt of prohibited vaccine (Varivax)	0	0.0	1	0.5

[a] Subjects may have been excluded for more than 1 reason.
Source: STN 125324/767.0, m5.3.5.1.3, CSR, Tables 14-44 and 14-45, p 208-209.

Clinical Reviewer Note:

- Although 295 subjects were included in the all-available population, only 294 subjects had a vaccination. Subject 000532 was included in the all-available immunogenicity population, but did not receive study vaccine. The definition of the all-available population does not require vaccination.
- Subjects were permitted to receive non-study vaccines concomitantly with study vaccination. Only subjects who received live vaccinations less than 28 days prior to study vaccination or non-live vaccinations less than 14 days prior to study vaccination were excluded from the evaluable immunogenicity population (see temporary delay criteria in section 6.1.3). Subjects who received non-study vaccines within 7 days after study vaccination were to be excluded, but no subjects received non-study vaccines within 7 days after study vaccination.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Group 3: IgG Geometric Mean Concentrations

For the seven original PCV7 serotypes, a single dose of Prevnar 13, when administered to children 5 through 9 years of age with a history of 3 or more prior doses of Prevnar, induced serotype-specific IgG GMCs that were non-inferior to the corresponding IgG GMCs induced by a fourth dose of Prevnar in children 12-15 months of age in a historical

control (pre-licensure PCV13 study 3005). The lower limit of the 95% CI for the GMC ratio was > 0.5 for each of the seven original PCV7 serotypes.

Table 9. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Original Seven PCV7 Serotypes, PCV13 Group 3c in Study 3011 Relative to PCV7 in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population

	PCV13 Group 3c (≥ 5 to < 10 yrs) (After single dose, Study 3011)			PCV7 (12-15 months) (Post-dose 4, Study 3005)			GMC Ratio: 3011/ 3005	95% CI
PCV7 Serotype	n	GMC	95% CI	n	GMC	95% CI		
4	169	8.5	7.2, 9.9	173	2.8	2.5, 3.2	3.0	2.5, 3.7
6B	171	53.6	45.5, 63.1	173	9.5	8.3, 10.9	5.7	4.6, 7.0
9V	171	9.5	8.4, 10.8	172	2.0	1.8, 2.2	4.8	4.1, 5.7
14	169	29.4	24.8, 34.8	173	8.2	7.3, 9.2	3.6	2.9, 4.4
18C	171	8.2	7.1, 9.5	173	2.3	2.1, 2.7	3.5	2.9, 4.3
19F	171	17.6	15.0, 20.7	173	3.3	2.9, 3.8	5.3	4.3, 6.6
23F	169	11.3	9.8, 13.0	173	4.5	3.9, 5.2	2.5	2.0, 3.1

Source: STN 125324/767.0, m5.3.5.1.3, CSR, Table 9-2, p 55.

For the 6 additional serotypes contained in PCV13, a single dose of Prevnar 13, when administered to children 5 through 9 years of age with a history of 3 or more prior doses of Prevnar, induced serotype-specific IgG GMCs that were non-inferior to the corresponding IgG GMCs induced by a fourth dose of Prevnar 13 in children 12-15 months of age in a historical control (pre-licensure PCV13 study 3005). The lower limit of the 95% CI for the GMC ratio was > 0.5 for each of the 6 additional pneumococcal serotypes.

Table 10. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Additional 6 Serotypes Contained in PCV13, PCV13 Group 3c in Study 3011 Relative to PCV13[a] in Study 3005 (Posttoddler) – Evaluable Immunogenicity Population

	PCV13 Group 3c (≥ 5 to < 10 yrs) (After single dose, Study 3011)			PCV13 (12-15 months) (Post-dose 4, Study 3005)			GMC Ratio: 3011/ 3005	95% CI
Additional Serotypes	n	GMC	95% CI	n	GMC	95% CI		
1	171	3.6	3.1, 4.2	1068	2.9	2.8, 3.1	1.2	1.1, 1.4
3	171	2.4	2.1, 2.7	1065	0.8	0.7, 0.8	3.2	2.8, 3.6
5	171	5.5	4.8, 6.3	1068	2.9	2.7, 3.0	1.9	1.7, 2.2
6A	169	21.5	18.2, 25.5	1063	7.1	6.8, 7.5	3.0	2.6, 3.5
7F	170	6.2	5.5, 7.1	1067	4.4	4.2, 4.6	1.4	1.2, 1.6
19A	170	17.2	15.0, 19.7	1056	8.4	8.1, 8.9	2.0	1.8, 2.3

[a] Includes immunogenicity data from three PCV13 lot groups combined in study 3005.
Source: STN 125324/767.0, m5.3.5.1.3, CSR, Table 9-3, p 56.

Group 4: Opsonophagocytic Geometric Mean Antibody Titers
For 12 of the 13 pneumococcal serotypes contained in PCV13, a single dose of PCV13, when administered to 10 thru 17 year olds with no prior pneumococcal vaccination

history, induced serotype-specific OPA antibody GMTs that were non-inferior to the corresponding OPA antibody GMTs induced by a single dose of PCV13 administered to 5 thru 9 year old children with a history of 3 or more prior doses of PCV7. The lower limit of the 95% CI for the GMT ratio (4c/3C) for 12 serotypes was > 0.5. The lower limit of the 95% CI for serotype 3 was 0.48; thus the primary endpoint for demonstrating non-inferiority of PCV13 in 10 thru 17 year olds, compared to PCV13 in 5 thru 9 year olds, was not met for serotype 3.

Table 11. Comparison of Pneumococcal OPA Antibody GMTs After Single PCV13 Vaccination for the 13 Vaccine Serotypes, PCV13 Group 4c Relative to PCV13 Group 3c – Evaluable Immunogenicity Population[a]

	PCV13 Group 4c (≥ 10 to < 18 yrs) (After single dose, Study 3011)			PCV13 Group 3c (≥ 5 to < 10 yrs) (After single dose, Study 3011)			GMT Ratio: 4c/ 3c	95% CI
	n	GMT	95% CI	n	GMT	95% CI		
PCV7 Serotypes								
4	188	6912	6101, 7831	181	4629	4017, 5334	1.5	1.24, 1.80
6B	183	14224	12316, 16427	178	14996	13164, 17083	0.9	0.78, 1.15
9V	186	4485	4001, 5028	180	4733	4203, 5328	0.9	0.80, 1.12
14	187	6894	6028, 7884	176	4759	4120, 5497	1.4	1.19, 1.76
18C	182	6263	5436, 7215	175	8815	7738, 10041	0.7	0.59, 0.86
19F	184	2280	1949, 2668	178	1591	1336, 1893	1.4	1.14, 1.81
23F	187	3808	3355, 4323	176	3245	2819, 3736	1.2	0.97, 1.42
Additional Serotypes								
1	189	322	275, 378	179	191	165, 221	1.7	1.36, 2.10
3	181	114	101, 130	178	203	182, 226	0.6	**0.48**, 0.67
5	183	360	298, 436	178	498	437, 568	0.7	0.57, 0.91,
6A	182	9928	8457, 11655	178	7514	6351, 8891	1.3	1.05, 1.67
7F	185	6584	5829, 7436	178	10334	9099, 11737	0.6	0.53, 0.76
19A	187	1276	1132, 1439	180	1180	1048, 1329	1.1	0.91, 1.28

[a] OPA antibody titers below the serotype-specific assay LLOQ were replaced with 0.5*LLOQ for the calculation of OPA antibody GMTs.
Source: STN 125324/767.0, m5.3.5.1.3, CSR, Table 9-18, p 83.

Clinical Reviewer Note:
Per FDA request, Wyeth performed a post-hoc sensitivity analysis in which OPA antibody GMTs were calculated using actual OPA antibody titers, 0.5*LLOQ, 0.75*LLOQ, 0.8*LLOQ, and 1.0*LLOQ in the place of those titers that fell below the serotype-specific assay LLOQ. The OPA antibody GMTs that were calculated were similar regardless of the OPA antibody titers used in place of titers that fell below the LLOQ; in addition, the study results did not change based on the results of this sensitivity analysis. Results presented in this review were based on calculations using 0.5*LLOQ in place of titers below the LLOQ; this is consistent with the mcOPA data shown in the package insert with regards to adults ≥ 50 years of age.

6.1.11.2 Analyses of Secondary Endpoints

For the seven original PCV7 serotypes, a single dose of Prevnar 13, when administered to pneumococcal vaccine naïve children 10 thru 17 years of age induced serotype-specific IgG GMCs that were non-inferior to the corresponding IgG GMCs induced by a fourth dose of Prevnar in children 12-15 months of age in a historical control (pre-licensure PCV13 study 3005). The lower limit of the 95% CI for the GMC ratio was > 0.5 for each of the seven original PCV7 serotypes.

Table 12. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Original Seven PCV7 Serotypes, PCV13 Group 4c in Study 3011 Relative to PCV7 in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population

	PCV13 Group 4c (≥ 10 to < 18 yrs) (After single dose, Study 3011)			PCV7 (12-15 months) (Post-dose 4, Study 3005)			GMC Ratio: 3011/ 3005	95% CI
PCV7 Serotype	**n**	**GMC**	**95% CI**	**n**	**GMC**	**95% CI**		
4	189	4.5	3.8, 5.3	173	2.8	2.5, 3.2	1.6	1.3, 2.0
6B	187	26.5	21.8, 32.2	173	9.5	8.3, 10.9	2.8	2.2, 3.6
9V	188	5.4	4.7, 6.1	172	2.0	1.8, 2.2	2.7	2.3, 3.2
14	188	18.5	14.4, 23.8	173	8.2	7.3, 9.2	2.3	1.7, 3.0
18C	187	6.6	5.5, 7.8	173	2.3	2.1, 2.7	2.8	2.3, 3.5
19F	185	13.9	11.7, 16.6	173	3.3	2.9, 3.8	4.2	3.4, 5.3
23F	184	15.4	12.6, 18.9	173	4.5	3.9, 5.2	3.4	2.7, 4.4

Source: STN 125324/767.0, m5.3.5.1.3, CSR, Table 9-12, p 74.

For the 6 additional serotypes contained in PCV13, a single dose of Prevnar 13, when administered to pneumococcal vaccine naïve children 10 thru 17 years of age induced serotype-specific IgG GMCs that were non-inferior to the corresponding IgG GMCs induced by a fourth dose of Prevnar 13 in children 12-15 months of age in a historical control (pre-licensure PCV13 study 3005). The lower limit of the 95% CI for the GMC ratio was > 0.5 for each of the 6 additional pneumococcal serotypes.

Table 13. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Additional 6 Serotypes Contained in PCV13, PCV13 Group 4c in Study 3011 Relative to PCV13[a] in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population

	PCV13 Group 4c (≥ 10 to < 18 yrs) (After single dose, Study 3011)			PCV13 (12-15 months) (Post-dose 4, Study 3005)			GMC Ratio: 3011/ 3005	95% CI
Additional Serotypes	**n**	**GMC**	**95% CI**	**n**	**GMC**	**95% CI**		
1	188	6.3	5.3, 7.5	1068	2.9	2.8, 3.1	2.2	1.9, 2.5
3	187	1.9	1.7, 2.1	1065	0.8	0.7, 1.8	2.5	2.2, 2.8
5	188	7.1	6.1, 8.1	1068	2.9	2.7, 3.0	2.5	2.2, 2.8
6A	188	16.9	14.1, 20.2	1063	7.1	6.8, 7.5	2.4	2.1, 2.7
7F	188	6.4	5.6, 7.3	1067	4.4	4.2, 4.6	1.5	1.3, 1.7
19A	188	17.7	15.5, 20.1	1056	8.4	8.1, 8.9	2.1	1.9, 2.4

[a] Includes immunogenicity data from three PCV13 lot groups combined in study 3005.

Source: STN 125324/767.0, m5.3.5.1.3, CSR, Table 9-13, p 74.

Clinical Reviewer Note: IgG GMCs achieved by 10 thru 17 year old subjects in study 3011 were compared to the IgG GMCs achieved by 12-15 month old toddlers in study 3005 rather than to the IgG GMCs achieved by 5 thru 9 year old subjects in study 3011, because the former are considered more directly related to effectiveness.

6.1.11.3 Subpopulation Analyses
See section 6.1.11.5 (Exploratory and Post Hoc Analyses).

6.1.11.4 Dropouts and/or Discontinuations

See Table 5 in section 6.1.10 (Study Population and Disposition) and Table 8 in section 6.1.10.1.3 (Subject Disposition).

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory Analysis:
Table 14 below shows the pre-vaccination OPA antibody titers for groups 3c and 4c. In both groups, the point estimate for serotype-specific fold rise in OPA antibody titers from pre- to post-vaccination was ≥ 4 (Data not shown, Tables 14-100 and 14-115 in the clinical study report). For group 4c, the fold rise ranged from 7.5 (95% CI 5.5, 10.2) for serotype 6B to 197.2 (143.6, 270.9) for serotype 6A. For group 3c, the fold rise ranged from 4.2 (95% CI 3.5, 5,0) for serotype 6B to 66.3 (46.8, 94.0) for serotype 6A.

Clinical Reviewer Note:
The pre- to post-vaccination fold rise in IgG GMCs was not generally consistent with the fold-rise in OPA antibody GMTs in groups 3 and 4. For instance, the IgG GMC fold-rise in both groups 3 and 4 were less than 4 for serotypes 3 and 5.

Table 14. Pneumococcal OPA Antibody GMTs Before Vaccination in Study 3011, PCV13 Group 4c and PCV13 Group 3c – Evaluable Immunogenicity Population[a]

	PCV13 Group 4c (≥ 10 to < 18 yrs)			PCV13 Group 3c (≥ 5 to < 10 yrs)		
	n	**GMT**	**95% CI**	**n**	**GMT**	**95% CI**
PCV7 Serotypes						
4	115	213	128, 354	120	198	122, 323
6B	137	2128	1649, 2746	166	3636	3215, 4113
9V	160	387	329, 456	149	456	382, 545
14	163	248	182, 339	166	589	455, 762
18C	166	141	96, 207	161	179	122, 262
19F	171	63	51, 79	172	170	133, 219
23F	150	36	24, 53	160	287	199, 416
Additional Serotypes						
1	187	10	10, 11	178	9	9, 10
3	179	13	11, 15	172	25	20, 32
5	181	16	15, 17	176	15	14, 15
6A	161	48	38, 62	163	111	82, 151
7F	147	652	505, 841	156	1092	852, 1399
19A	179	44	34, 57	177	90	71, 115

[a] OPA antibody titers below the serotype-specific assay LLOQ were replaced with 0.5*LLOQ for the calculation of OPA antibody GMTs.
Source: Adapted from STN 125324/767.0, m5.3.5.1.3, CSR, Tables 14-90 & 14-105, p254 & 279.

Clinical Reviewer Note:
Subjects in each study group were noted to have pre-existing OPA antibody titers prior to vaccination. Some pre-existing antibodies to the seven PCV7 serotypes in study group 3c may be expected due to prior PCV7 vaccination. For the 6 additional serotypes in both groups and for the PCV7 serotypes in group 4c, pre-existing antibodies may be the result of prior colonization or infection. The clinical relevance of the measured pre-vaccination OPA antibody titers is unclear, as the OPA antibody titer that correlates with clinical protection against IPD is not known.

Exploratory Analysis: Proportion of subjects achieving an OPA antibody titer ≥ LLOQ
The proportion of subjects achieving an OPA antibody titer ≥ LLOQ was high in both groups 3 and 4 (Data not shown – Tables 9-8 and 9-11 in clinical study report) for each of the thirteen vaccine serotypes. In group 3, 97.8% to 100% (lower limit of 95% CIs ranging from 94.4% to 98.0%) of subjects achieved OPA antibody titers against the thirteen vaccine serotypes that were ≥ the serotype-specific mcOPA assay LLOQ. In group 4, 94.5% - 100% (lower limit of 95% CIs ranging from 90.2% to 98.1%) of subjects achieved OPA antibody titers against the thirteen vaccine serotypes that were ≥ the serotype-specific mcOPA assay LLOQ.

Post-Hoc Analyses By Sex and Race
Some differences were noted in post-hoc non-inferiority analyses performed by sex and race; these post-hoc analyses were performed on the all-available population.

Although immune responses among males and females appeared to be similar, direct statistical comparisons were not made. Likewise, immune responses among the different races were not compared statistically. Yet, no clear or consistent difference in immune response by race was observed; the confidence intervals of subgroups other than white subjects were small and resulted in wide overlapping intervals. Unless otherwise specified below, the lower limit of the geometric mean ratio for the subset analyses by sex and race was > 0.5.

IgG GMC Comparisons in Group 4c of Study 3011 and Study 3005 (Data not shown)
- When IgG GMCs for the 7 common serotypes among subjects of "other races" were compared between group 4c in study 3011 to study 3005, the non-inferiority (NI) criterion was not met for serotypes 4, 6B and 23F (Table 14-173, p 331 in CSR). However, the sample size was small (n=9-10 in each group) in this analysis, resulting in wide confidence intervals.

OPA Antibody GMT Comparisons in Group 4c and Group 3c in Study 3011 (Data not shown)
- When OPA antibody GMTs among males were compared between groups 4c and 3c in study 3011, the NI criterion was not met for serotypes 3, 5, and 7F (Table 14-179,

p 334 in CSR). The NI criterion was also not met for serotype 3 in the primary analysis (Table 11).

- When OPA antibody GMTs among females were compared between groups 4c and 3c in study 3011, the NI criterion was not met for serotypes 18C, 3 and 5 (Table 14-180, p 335 in CSR). The NI criterion was also not met for serotype 3 in the primary analysis (Table 11).
- When OPA antibody GMTs among blacks were compared between groups 4c and 3c in study 3011, the NI criterion was not met for serotypes 18C, 3, and 5 (Table 14-182, p 337 in CSR).
- When OPA antibody GMTs among subjects of other races were compared between groups 4c and 3c in study 3011, the NI criterion was not met for serotypes 6B, 9V, 18C, 19F, 1, 3, 5, 6A, 7F, and 19A (Table 14-183, p 338 in CSR).

Post-Hoc Immunogenicity Analyses by Non-Study Concomitant Vaccination Status
Post-hoc analyses, which were limited by small numbers of subjects who received non-study concomitant vaccinations, suggest that concomitant administration of Prevnar 13 with non-study vaccinations could result in some diminishment of IgG and OPA antibody antibody response for some serotypes compared to the corresponding antibody responses when Prevnar 13 is administered alone, particularly among group 4 subjects (10 through 17 years of age). For example, the point estimates and 95% confidence intervals for the OPA antibody GMT ratios (received/did not receive concomitant vaccine) were below 1 for some serotypes (i.e., Group 3: 9V and 6A; Group 4: 3, 4, 6A, 6B, 7F, 18C, and 23F) (Data not shown, Tables 22–23 and 26-27, STN 125324/767.3, m 1.11.3). For primary objective comparisons between study 3011 subjects who received non-study concomitant vaccines and the historical control (study 3005 post-dose 4), the lower limit of the 95% confidence intervals for the geometric mean ratios (study 3011 subjects with any non-study vaccine / study 3005 post-dose 4 historical control) were greater than 0.5 for all serotypes within group 3 and for 9 serotypes within group 4 (all except 3, 5, 7F, and 18C) (Data not shown, Tables 2-5 and 10-11, STN 125324/767.3, m1.11.3). This suggests that among children 10 through 17 years of age, concomitant vaccination of Prevnar 13 with routine pediatric vaccines may result in an inferior immune response for some serotypes compared to the immune response achieved by those who receive Prevnar alone.

Clinical Reviewer Note:
Evaluation of any potential immunologic interference when Prevnar 13 is concomitantly administered with routine preventive vaccines in persons 5 through 17 years of age was not a pre-specified study objective in study 3011. Post-hoc analyses suggest that concomitant administration of Prevnar 13 with non-study vaccinations may result in some diminishment of IgG and OPA antibody responses for some serotypes compared to the corresponding antibody responses when PCV13 is administered alone. However, these analyses were limited by small numbers of subjects and inconsistent and incomplete data collection regarding concomitant vaccinations in this study. Thus, there are insufficient data to assess the immunogenicity of Prevnar 13 when administered with concomitant pediatric vaccinations in children 6 through 17 years of age. Language was added to the package insert to indicate that there are insufficient data to assess concomitant administration of Prevnar 13 with Human Papillomavirus Vaccine (HPV),

Meningococcal Conjugate Vaccine (MCV4) and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap). Please see section 11.6 for a discussion regarding recommendations on postmarketing actions.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please see section 6.1.7 for information regarding safety monitoring. The safety analysis population included all subjects who received one dose of PCV13 (N=294 in groups 3e+3c; N=298 in groups 4e+4c).

Immediate reactions (i.e., those occurring within 30 minutes after study vaccination) were collected and reported along with other unsolicited AEs. However, the specific time-to-onset of immediate reactions was not recorded; therefore reactions that occurred within 30 minutes of vaccination could not be distinguished from other unsolicited AEs.

6.1.12.2 Overview of Adverse Events

Solicited Local Reactions

The most common solicited local reaction in both groups was injection site tenderness, followed by redness in group 3 (5 thru 9 year olds) and swelling in group 4 (10 thru 17 year olds) (Table 15). Nearly 20% of 5 thru 9 year olds and 44% of 10 thru 17 year olds experienced significant tenderness. Severe redness and severe swelling (> 7cm in diameter) were each reported in 2-3% of subjects.

The rate of significant tenderness was noted to be higher in 10 thru 17 year olds compared to 5 thru 9 year olds. Rates of swelling were similar between the two groups. Rates of any redness and mild to moderate redness were higher among 5 thru 9 year olds compared to 10 thru 17 year olds.

Table 15. Subjects in Study 3011 Reporting Local Reactions Within 7 Days of Vaccination with PCV13

	Group 3e+3c (≥ 5 to < 10 yrs)			**Group 4e+4c (≥ 10 to < 18 yrs)**		
	N	**n**	**%**	**N**	**n**	**%**
Tenderness						
Any	265	230	86.8	283	252	89.0
Significant[a]	221	43	19.5	242	106	43.8
Swelling[b]						
Any	226	85	37.6	233	86	36.9
Mild	220	48	21.8	221	50	22.6
Moderate	219	48	21.9	226	48	21.2
Severe	211	7	3.3	214	4	1.9
Redness[b]						
Any	233	100	42.9	232	70	30.2
Mild	226	63	27.9	226	48	21.2
Moderate	218	48	22.0	221	31	14.0
Severe	212	7	3.3	213	4	1.9

[a] Significant = present and interfered with limb movement.
[b] Mild: 0.5 – 2.0 cm; Moderate: 2.5 – 7.0 cm; Severe: > 7.0 cm.
Source: Adapted from STN 125324/767.0, m5.3.5.1.3, CSR, Tables 10-1 & 10-2, p 90.

Clinical Reviewer Note: Solicited local and systemic adverse events were to be monitored and recorded by the subject's parent or legal guardian for all age groups in study 3011. The rates of solicited local reactions were higher in general in the exploratory subset compared to the confirmatory cohort of group 3. Rates of significant tenderness in groups 3 and 4 are noted to be higher than the rates observed after a single dose in children 15 through 59 months of age (groups 1 and 2 of study 3011) but similar to the rates of any limitation of arm movement and any pain observed in adults 50-59 years of age in study 6115A1-004 (see PCV13 package insert, Table 9). The rates of significant tenderness in group 4 are also similar to rates of significant tenderness observed following the administration of some routine vaccines in this age group, such as Boostrix (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular pertussis Vaccine, Adsorbed) and Gardasil (Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant).

The mean duration of local reactions ranged from 1.9 to 2.4 days (SD 1-2 days) in group 3 and from 1.3 to 2.2 days (SD 1-2 days) in group 4 (Table 16). In group 3, any tenderness and significant tenderness peaked on days 1 and 2 after vaccination, respectively. In group 4, any tenderness and significant tenderness peaked on day 2. Any swelling, any redness, and moderate to severe swelling peaked on day 2 in groups 3 and 4; moderate to severe redness peaked on days 2 and 3 in groups 3 and 4. Rates of local reactions diminished considerably each day after the peak rate was reached (Data not shown, Tables 14-125- 14-136, p 307-312 and Fig 14-170 and 14-171, p 772-773).

Table 16. Duration[a] (Days) of Solicited Local Reactions

	Group 3e+3c (≥ 5 to < 10 yrs)					**Group 4e+4c (≥ 10 to < 18 yrs)**				
	N	**n**	**Mean**	**SD[b]**	**Range**	**N**	**n**	**Mean**	**SD**	**Range**
Tenderness	265	230	2.4	1.8	1-18	283	252	2.9	1.7	1-11
Redness	233	100	1.9	1.1	1-5	232	70	2.0	1.3	1-7
Swelling	226	85	2.1	1.5	1-8	233	86	2.3	2.2	1-77

[a] Duration calculated in days as the difference from the start of the first reported reaction to resolution of the last reported reaction, inclusive.
[b] SD = standard deviation
Source: Adapted from STN 125324/767.0, m5.3.5.1.3, CSR, Tables 10-5 and 10-6, p 92-93.

Solicited Systemic Adverse Events
The most common solicited systemic AE was irritability followed by decreased appetite and increased sleep in group 3 (5 thru 9 yr olds); in group 4 (10 thru 17 yr olds), the most common solicited systemic adverse event was increased sleep followed by irritability, decreased appetite and decreased sleep. Higher

proportions of 5 thru 9 yr old subjects reportedly used medications to treat and/or prevent symptoms compared to 10 thru 17 yr olds (Table 17).

Table 17. Subjects in Study 3011 Reporting Systemic Adverse Events Within 7 Days of Vaccination with PCV13

	Group 3e+3c (≥ 5 to < 10 yrs)			Group 4e+4c (≥ 10 to < 18 yrs)		
	N	**n**	**%**	**N**	**n**	**%**
Fever						
Any Fever (≥ 38.0°C)	214	13	6.1	214	12	5.6
38.0°C ≤ x ≤ 39.0°C	212	9	4.2	214	11	5.1
39°C < x ≤ 40.0°C	212	5	2.4	212	1	0.5
> 40°C	210	1	0.5	212	1	0.5
Decreased appetite	227	52	22.9	223	51	22.9
Irritability	234	73	31.2	234	59	25.2
Increased sleep	226	48	21.2	229	61	26.6
Decreased sleep	212	12	5.7	224	42	18.8
Hives (urticaria)	213	4	1.9	214	3	1.4
Use of medication to treat symptoms	232	88	37.9	232	66	28.4
Use of medication to prevent symptoms	225	58	25.8	225	47	20.9
Use of medication to treat or prevent symptoms	237	107	45.1	236	78	33.1
Use of medication to treat and prevent symptoms	220	35	15.9	221	29	13.1

Source: Adapted from STN 125324/767.0, m5.3.5.1.3, CSR, Tables 10-7 and 10-8, p 94-95 and STN 125324/767.2, m1.11.3, Table 54 (p 99).

The mean duration of solicited systemic adverse events and use of antipyretic medications ranged from 1.2 to 2.8 days (SD 1-3 days) in group 3 and from 1.0 to 2.8 days (SD 0-3 days) in group 4 (Table 18). In general, solicited systemic adverse events peaked on days 2 or 3 and the use of medications to prevent and/or treat symptoms peaked on Days 1 or 2 after vaccination (Data not shown, Tables 14-139 thru 14-158, p 314-323 in CSR).

Table 18. Duration[a] (Days) of Solicited Systemic Adverse Events

	Group 3e+3c (≥ 5 to < 10 yrs)					Group 4e+4c (≥ 10 to < 18 yrs)				
	N	**n**	**Mean**	**SD[b]**	**Range**	**N**	**n**	**Mean**	**SD**	**Range**
Any Fever ≥ 38°C	214	13	2.2	2.6	1-10	214	12	1.7	1.2	1-4
Decreased appetite	227	52	2.0	2.0	1-10	223	51	2.6	2.6	1-13
Irritability	234	73	2.1	1.6	1-8	234	59	2.7	3.3	1-16
Increased sleep	226	48	2.1	2.2	1-10	229	61	2.8	3.0	1-16
Decreased sleep	212	12	2.8	3.3	1-11	224	42	2.7	2.8	1-14
Hives (urticaria)	213	4	2.3	1.9	1-5	214	3	1.0	0.0	1-1
Use of medication to treat symptoms	232	88	1.7	1.4	1-11	232	66	1.7	1.4	1-7

	Group 3e+3c (≥ 5 to < 10 yrs)					Group 4e+4c (≥ 10 to < 18 yrs)				
	N	**n**	**Mean**	**SD[b]**	**Range**	**N**	**n**	**Mean**	**SD**	**Range**
Use of medication to prevent symptoms	225	58	1.2	0.5	1-3	225	47	1.7	1.5	1-9

[a] Duration calculated in days as the difference from the start of the first reported reaction to resolution of the last reported reaction, inclusive.
[b] SD = standard deviation.
Source: Adapted from STN 125324/767.0, m5.3.5.1.3, CSR, Tables 10-9 and 10-10, p 96-97.

Unsolicited Adverse Events Through 1 Month Post-Vaccination
The incidence of any unsolicited AEs reported through 1 month post-vaccination was 19.4% (57/294) in group 3 and 24.2% (72/298) in group 4 (Data not shown – Table 10-11 and 10-12 in CSR). In both groups 3 and 4, the most frequently reported MedDRA preferred terms were under the MedDRA system organ class (SOC) Infections and Infestations (30-31 subjects, 10.2% - 10.4%). In group 3, the most frequently reported individual MedDRA preferred terms were cough (10, 3.4%), vomiting (8, 2.7%), pyrexia (7, 2.4%), and pharyngitis streptococcal (6, 2.0%). In group 4, the most frequently reported individual MedDRA preferred terms were headache (10, 3.4%), cough (5, 1.7%), pharyngitis (5, 1.7%), influenza (5, 1.7%), oropharyngeal pain (5, 1.7%), and sinusitis (5, 1.7%).

Two subjects in group 3 reported severe or life-threatening AEs (appendicitis and eye injury), which were considered un-related to the study vaccine. This reviewer agrees with this assessment. There were no severe or life-threatening AEs in group 4.

Three subjects (1.0%) in group 3 and 3 subjects (1%) in group 4 reported a total of 13 AEs within 1 month after vaccination that were considered related to study vaccination (6 events in group 3 and 7 events in group 4). In group 3, related AEs were diarrhea (1), nausea (1), vomiting (1), pyrexia (1), and headache (2). In group 4, related AEs were nausea (1), injection site pain (1), injection site pruritis (1), back pain (1), dizziness (1) and headache (2).

Unsolicited Adverse Events Reported at the 6-Month Follow-Up Phone Contact
The incidence of unsolicited AEs reported at the 6-month telephone contact was 2.4% (7/294) in group 3 and 1.7% (5/298) in group 4. In group 3, the AEs reported were myopia, irritable bowel syndrome, asthma, bronchial hyperreactivity and rhinitis allergic. In group 4, the AEs reported were diarrhea, migraine, depression, asthma and rhinitis allergic. There were neither severe or life-threatening AEs nor related AEs in groups 3 or 4 at the 6-month follow-up contact.

6.1.12.3 Deaths

There were no deaths during this study.

6.1.12.4 Nonfatal Serious Adverse Events

One SAE was reported within 1 month after vaccination by 1 subject in group 3. Subject 034-002190 reported severe appendicitis on day 1; however, this event was not considered related to study vaccination by the study investigator and it resolved. This clinical reviewer agrees with the study investigator's assessment. There were no SAEs reported in group 4 through 1 month post-vaccination. At the 6-month follow-up, 1 subject in group 4 reported moderate asthma on day 161; this SAE was not considered related to study vaccination by the study investigator and it resolved. This clinical reviewer agrees with the study investigator. There were no SAEs reported at the 6-month follow-up in group 3.

6.1.12.7 Dropouts and/or Discontinuations

There were no AEs that led to withdrawal from the study in groups 3 or 4.

Study 3011 Addendum: Safety Data From Cohort 2 of Groups 1 and 2

A safety addendum was provided for study 3011 which includes all safety data for cohort 2 subjects in Study groups 1 and 2. Cohort 2 subjects consist of the additional subjects enrolled into groups 1 and 2 as part of amendment 3 of the study protocol, which expanded the sample size of each group within study 3011 to a total of 300 subjects. Safety data for this cohort were not yet available during the review of the initial Prevnar 13 BLA. Thus, these data were submitted to this supplement for review.

For "all subjects" in cohort 2, the demographics and the number of prior Prevnar doses were not fundamentally different between Cohorts 1 and 2 (Data not shown, Tables 3-10 and 9, STN 125324/767.2, m5.3.5.1.3 and Tables 8-10 and 10-1, STN 125324/0.67, m5.3.5.1, CSR). It is noted that, during the study, a higher proportion of "all subjects" in cohort 2 received a non-study vaccine (81.3% in group 1 and 52.1% in group 2) compared to cohort 1 (54% in group 1 and 28.7% in group 2) (Data not shown, Table 6-11, STN 125324/767.2, m5.3.5.1.3 and Table 15.9, 125324/0.67, m5.3.5.1, CSR).

There were no deaths or withdrawals due to an AE in this study. A total of 7 subjects reported SAEs within 48 to 162 days post-vaccination. After dose 1, asthma was reported in 1 group 1 subject and pneumonia and wheezing were reported in 1 group 2 subject. After dose 2, 6 SAEs (GI rotavirus, bronchiolitis, RSV bronchiolitis, Staphylococcal infection, and near drowning) were reported for 6 subjects in group 1. None of these SAEs were considered by the principal investigator or applicant to be related to study vaccine. This clinical reviewer agrees with the assessment made by the study investigator. For cohorts 1 and 2 at the 6-month safety follow up, SAEs were reported by 3 subjects in group 1 (vomiting, abdominal injury, febrile convulsion, and nephritic syndrome) and 1 subject in group 2 (status asthmaticus); none were considered by the principal investigator or applicant to be related to vaccination. This clinical reviewer agrees with the assessment made by the study investigator.

With a few exceptions, the post-dose 1 and post-dose 2 safety data for cohort 2 subjects did not differ fundamentally from the safety data for cohort 1 subjects, which are

currently described in the Prevnar 13 package insert. It was noted that rates of injection site redness within 4 and 7 days after dose 1 were lower among cohort 2 compared to cohort 1 subjects (i.e., any redness: 18.9% vs 38.8% within 7 days) (Data not shown, Tables 4-2, 28 and 6.40, STN 125324/767.2, m5.3.5.1.3 and Tables 10-2 and 15.18, STN 125324/0.67, m5.3.5.1 CSR). In addition, rates of injection site swelling and redness within 7 days of dose 1 were lower among subjects with 3 prior PCV7 doses in Cohort 2 compared to cohort 1 (swelling in Cohort 2: 15.0% vs swelling in Cohort 1: 35.5%; redness in Cohort 2: 10.0% vs redness is Cohort 1: 46.9%) (Data not shown, Table 4-5, 125324/767.2, m5,3,5,1,3 and Table 10-7, 125324/0.67, m5.3.5.1, CSR). A similar trend was seen with rates of local reactions (tenderness, swelling, and redness) within 4 and 7 days after dose 2 (Data not shown, Tables 4-6 and 6.49, STN 125324/767.2, m5.3.5.1 and Tables 10-9 and 15.20, 125324/0.67, m5.3.5.1, CSR).

Adverse events reported after dose 1 and 2 which were considered to be related to Prevnar 13 included the following in Group 1: (vomiting, viral infection, viral rash, viral upper respiratory tract infection, and cough). Related AEs reported after dose 1 in group 2 included the following: (diarrhea, injection site pruritis, injection site reaction, and headache.

A request was made to the Applicant that the safety data for groups 1 and 2 in the Prevnar 13 package insert be revised to reflect pooled safety data for cohorts 1 and 2; these pooled data were also requested to be submitted to this supplement.

Post-Hoc Analyses By Sex and Race (Data not shown: Tables 14-254 thru 14-261 and 14-374 thru 14-383 in Clinical Study Report).
Statistical comparisons were not included in the post-hoc descriptive safety data by sex and race. However, some differences were observed and are described below. Of note, the denominators of some subgroups were small. For the “other races” subgroup, the denominators were considered too small for the purpose of evaluating for trends.

<u>Solicited Local Reactions within 7 days of vaccination</u>:

1. Compared to male subjects, a higher proportion of female subjects were reported to experience the following:
   - any and significant tenderness in groups 3 and 4.
   - any swelling in groups 3e and 4; and
   - any redness in groups 3e and 4c.

2. Compared to black subjects, a higher proportion of white subjects were reported to experience the following:
   - any tenderness in group 4c and significant tenderness in groups 3c and 4
   - any swelling in groups 3e and 4e
   - any redness in groups 3 and 4.

3. In both the exploratory and confirmatory cohorts of groups 3 and 4, the proportion of subjects with moderate swelling or moderate redness were higher on average among females and whites compared to males and blacks, respectively.

Solicited Systemic Adverse Events within 7 days of vaccination:

1. Compared to males, a higher proportion of females were reported to experience the following:
   - irritability in group 4c;
   - decreased appetite in group 3c;
   - increased sleep in groups 3e and 4e; and
   - decreased sleep in group 4e.

2. Compared to black subjects, a higher proportion of white subjects were reported to experience the following:
   - irritability in groups 3e and 4e; and
   - decreased sleep and increased sleep in group 4.
   - In group 3, there were some higher rates of use of medication to treat and/or prevent symptoms among females compared to males.

3. There were no other remarkable differences or clear trends noted in the rates of solicited adverse events by race or sex.

Post-Hoc Safety Analyses by Non-Study Concomitant Vaccination Status
There appeared to be more moderate redness reported within 4 days of vaccination in group 3 subjects who received any concomitant vaccination compared to group 3 subjects who received no concomitant vaccinations (26.7% vs 16.8%, Table 38, STN 125324/767.2, m1.11.3). There were no other fundamental differences noted in rates of solicited local or systemic adverse reactions between subjects who received concomitant vaccinations and subjects who received Prevnar 13 alone.

7. INTEGRATED OVERVIEW OF EFFICACY

This review focuses on the single study submitted to this sBLA (study 6096A1-3011). An integrated summary of efficacy is not presented, because this submission consists of one study.

7.1.8 Persistence of Efficacy

Persistence of antibodies beyond 1 month after a single dose of Prevnar 13 was not evaluated in 5 through 17 year olds in this submission. However, it was noted that subjects in both study groups had pre-existing OPA antibody titers, which may be due to persistent antibodies following prior PCV7 administration and/or natural exposure to *S. pneumoniae*. Without a defined correlate of protection (i.e., a defined OPA antibody titer that correlates with protection against IPD), the clinical significance of these pre-existing antibody levels is not known.

7.1.9 Product-Product Interactions

Please refer to the Clinical Reviewer Note in section 6.1.11.5.

7.1.10 Additional Efficacy Issues/Analyses

7.1.11 Efficacy Conclusions

A total of 182 children 5 through 9 year olds and 190 children 10 through 17 year olds were included in the evaluable (per-protocol) immunogenicity populations for the confirmatory cohorts. The primary effectiveness (immunogenicity) endpoints were met for each of the thirteen vaccine serotypes for children 5 through 9 years of age and for 12 of the 13 vaccine serotypes for children 10 through 17 years of age (except serotype 3). The IgG GMCs induced by PCV13 among children 5 through 9 year olds were shown to be non-inferior to the post-dose 4 IgG GMCs among PCV7 recipients in study 3005 for the 7 common serotypes and among PCV13 recipients in study 3005 for the 6 additional serotypes (Tables 9 and 10, page 28). The non-inferiority criterion required that the GMC ratio (study 3011/study 3005) be greater than 0.5 (i.e., lower limit of the 2-sided 95% confidence interval (CI) for the GMT ratio > 0.5) for each of the 13 serotypes. For children 10 through 17 years olds, the OPA antibody GMTs were shown to be non-inferior to the OPA antibody GMTs achieved among PCV13 recipients 5 through 9 years of age in study 3011 for 12 of the 13 vaccine serotypes (except serotype 3) (Table 11, page 29). The non-inferiority criterion required that the GMT ratio (10 thru 17 yr olds / 5 thru 9 yr olds) be greater than 0.5 (i.e., lower limit of the 2-sided 95% CI for the GMT ratio > 0.5) for each of the 13 serotypes. The non-inferiority criterion was missed by a small margin for serotype 3.

8. Integrated Overview of Safety

This review focuses on the single study submitted to this sBLA (study 6096A1-3011). An integrated summary of safety is not presented, because this submission consists of one study.

8.5.5 Product-Product Interactions

There were insufficient data to assess the safety of Prevnar 13 when administered with concomitant pediatric vaccinations in children 6 through 17 years of age. The safety of concomitant administration of Prevnar 13 with routine preventive vaccines in persons 5 through 17 years of age was not a pre-specified objective in study 3011.

8.6 Safety Conclusions

A total of 294 children 5 through 9 year olds and 298 children 10 through 17 years olds were included in the safety population (which included subjects enrolled into both the exploratory and confirmatory study cohorts). Safety parameters evaluated in each study included unsolicited adverse events (AEs) and pre-specified solicited AEs (local injection site reactions and systemic AEs). The most common solicited local reaction was injection site tenderness, with nearly 20% of 5 through 9 year olds and 44% of 10 through 17 years olds experiencing significant tenderness (defined as limitation of arm movement). These rates of significant tenderness are comparable to rates observed with some routine pediatric vaccines administered to children in this age group, such as Boostrix and

Gardasil. The most common solicited systemic AEs included irritability, increased sleep and decreased appetite. There were no reported deaths, no adverse events that resulted in withdrawal from the study, and no serious adverse events which were considered related to the study vaccination during the study period.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Prevnar 13 is currently assigned a Pregnancy Category B. Please refer to Prevnar 13 PI or the Toxicology review for STN 125324/262 for more information. There were no reported pregnancies during study 3011.

9.1.2 Use During Lactation

As explained in the current Prevnar PI, it is not known whether Prevnar 13 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prevnar 13 is administered to a nursing woman.

9.1.3 Pediatric Use and PREA Considerations

Prevnar 13 was approved for use in children 6 weeks through 5 years of age on February, 24, 2010 for the following indications:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A. (1.1)

For the purposes of PREA, the pediatric population includes children from birth through 16 years of age. The Applicant previously received a waiver for PREA requirements to evaluate prevention of otitis media in children 6 through 16 years of age due to the low incidence of otitis media in this age group. For the IPD and otitis media indications, studies in children from birth to < 6 weeks of age were waived, and studies in children 6 weeks through 5 years of age have been completed. Thus, the pediatric study requirement in children 6 through 16 years of age was deferred for the IPD indication. Although this deferred study, study 3011, was only required to enroll children 6 through 16 years of age, the Applicant chose to enroll children 5 through 17 years of age.

Submission of this supplement, which contains the final report of deferred pediatric study 3011 to evaluate the safety and immunogenicity of Prevnar 13 in pediatric patients 6 through 16 years of age, fulfills the single post-marketing requirement (PMR) under PREA specified in the February 24, 2010 approval letter for the original Prevnar 13 BLA. A presentation of the results of the age expansion component of study 3011 was made to the FDA Pediatric Review Committee (PeRC) on December 12, 2012. The Committee concurred that the PMR for this study is fulfilled.

PREA does not otherwise apply to this application, as this application does not provide for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

9.1.4 Immunocompromised Patients

The effectiveness of Prevnar 13 has not been demonstrated in children or adults who are at increased risk for IPD, including immunocompromised individuals (see section 2.1). ----------(b)(4)----------:

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9.1.5 Geriatric Use

Prevnar 13 was approved on December 30, 2011 for use in adults 50 years of age and older for the active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. This approval was based on an immunologic surrogate endpoint through the accelerated approval regulations. As a condition of an accelerated approval, the applicant has an ongoing randomized, placebo-controlled clinical endpoint study, the Community-Acquired Pneumonia Immunization Trial in Adults (CAPITA), to confirm the clinical benefit of a single dose of Prevnar 13 in this age group. The results from this study are anticipated sometime in 2013. Please refer to the clinical review for STN 125324/262 or the package insert for more information regarding the safety and immunogenicity data available in the geriatric population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Data are not available regarding the use of a single dose of Prevnar 13 in children 10 through 17 years of age who previously completed a 3 or 4 dose infant series of a pneumococcal conjugate vaccine. At the time that study 3011 was conducted, children in

this age group would not have received PCV7 (approved in 2000) or PCV13 (approved in 2010). The safety of Prevnar 13 in this population can be extrapolated from the available safety data in children 5 through 9 years of age who previously completed a 3 or 4 dose infant series of Prevnar 13.

10. CONCLUSIONS

The available safety and immunogenicity data from 5 through 17 year olds in study 6096A1-3011 support the approval of Prevnar 13 in children 6 through 17 years of age for the prevention of IPD caused by the thirteen serotypes contained in the vaccine. Please refer to section 11 for more information regarding risk-benefit considerations and recommendations.

With regards to the proposed otitis media indication, the immunogenicity comparisons in study 3011 to the post-dose 4 immune responses in study 3005 are not applicable to the determination of protection against disease endpoints other than IPD. Thus, ELISA IgG data can only be used to bridge back to the demonstration of effectiveness of Prevnar 13 against IPD. The efficacy of Prevnar 13 against otitis media was also not assessed in a pre-licensure clinical endpoint study in children 6 through 17 years of age. Therefore, the proposed otitis media indication in this age group was not approved. Of note, as mentioned previously, with regards to PREA, the requirement to study the efficacy of Prevnar 13 against otitis media in children 6 through 16 years of age was waived due to the low incidence of otitis media in this age group.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Considerations of risk-benefit in this review were evaluated separately for healthy children and children at increased risk of IPD. These considerations represent a qualitative evaluation based on the judgment of the clinical reviewer. The factors to consider in risk-benefit considerations for Prevnar 13 in children and adolescents 6 through 17 years of age include those described below (also see Table 19).

Immunologic bridging and safety results from study 3011 support the safety and effectiveness of this vaccine, respectively, in children 6 through 17 years of age.

1. For *healthy* children 6 through 17 years of age with no underlying medical conditions or demographic characteristics that increase the risk of IPD, there is no clear benefit of routine vaccination with Prevnar 13 (as discussed below). The appropriate use of this vaccine in this age group will be based on risk/benefit analysis by the practitioner taking into account any risk factors for invasive pneumococcal disease in the individual patient.

   In the context of no increased risk of IPD, practitioners may choose not to routinely vaccinate individuals in this population because of the following considerations:
   - *Low incidence of disease in this age group*:

    - In 2010, the rate of IPD in the US among 6 through 17 year olds was very low (2.2 cases per 100,000; a total of 111 cases). Compared to rates among other age groups, this rate was the lowest. In 2010, IPD rates were highest among adults ≥ 65 years of age (36.4 cases per 100,000) and infants < 1 year of age (34.2 cases per 100,000).
- *No unmet medical need in healthy 6 through 17 year olds:*
    - Epidemiologic data suggest that PCV-unimmunized children in the US in non-vaccine-targeted age groups benefit from the indirect effects of routine PCV immunization of children ≤ 5 years of age. Since 2000, all infants in the US routinely receive a 4-dose series of a pneumococcal conjugate vaccine (PCV); in addition, pneumococcal vaccine naïve children ≤ 5 years of age have been receiving PCV via a catch-up immunization schedule.
    - Children ≥ 2 years of age at increased risk of IPD may receive PPSV23. PPSV23 includes 11 pneumococcal serotypes that are not contained in PCV13 (however, PPSV23 lacks serotype 6A which is included in PCV13).
    - Effective antibiotic therapies are available to treat IPD in 6 thru 17 year olds.

2. For children 6 through 17 years of age with *risk factors* for *IPD*, PCV13 may provide a more favorable risk/benefit profile compared to the use of PCV13 in healthy 6 through 17 year olds. However, there are no safety or effectiveness data available with Prevnar 13 in children with risk factors for IPD. In addition, the optimal number of doses of PCV13 and the interval between doses have not been established in this population. There are also no data available in this sBLA to address a recommended schedule for Prevnar 13 in the context of the availability of Pneumovax 23.

11.2 Risk-Benefit Summary and Assessment

The safety and effectiveness of Prevnar 13 for the prevention of IPD in children 6 through 17 years of age has been demonstrated based on data submitted to this sBLA. Although there is no clear benefit of routinely administering Prevnar 13 to all children 6 through 17 years of age, the risk-benefit profile is favorable under certain circumstances, such as for individuals determined to be at high risk for IPD (i.e., due to underlying medical conditions or demographic characteristics). There are no safety or immunogenicity data available that support the current proposed dosage and administration regimen of Prevnar 13 in high risk groups. The appropriate use of Prevnar 13 in this age group will be based on risk/benefit assessment by the practitioner for the individual patient.

Table 19. Risk-Benefit Considerations of Prevnar 13 in Children and Adolescents 6 through 17 Years of Age.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	IPD is a serious and life-threatening condition which occurs at very low rates (the lowest among all age groups) in healthy 6 through 17 year olds. IPD rates are higher among high-risk children in this age group.	Children 6 through 17 years of age with certain underlying conditions or demographic characteristics are at increased risk for IPD.
Unmet Medical Need	• Routine use of PCV13 is not recommended for healthy children ≥ 5 yrs of age. All infants routinely receive PCV13. The indirect effects of vaccinating children ≤ 5 years of age with a PCV include the prevention of IPD among children 6 through 17 years of age. • There is a permissive recommendation by the ACIP for PCV13 in children 6 through 17 years of age who are at increased risk of IPD. • Effective antibiotic therapy is available for the treatment of IPD in this age group; however, antibiotic resistance is increasingly common making treatment more difficult.	• In children 6 through 17 years of age at increased risk of IPD, there may be a need for PCV13 in addition to PPSV23. • In healthy children 6 to 17 years of age, there is no clear benefit for routine vaccination with PCV13 .
Clinical Benefit	• Clinical endpoint studies in healthy children 6 through 17 years of age are not feasible because of the low rate of disease. • Immunogenicity studies are limited because there is no established correlate of protection, and there is no consensus on the most clinically relevant immune response level which may correlate with protection.	• Effectiveness data are limited because bridging was based on IgG ELISA antibody concentrations, which include the measurement of non-functional antibodies in older children. • Designing an adequate and well controlled study to demonstrate the effectiveness of PCV13 in high risk groups has not been feasible.
Risk	• The most common risks of vaccination with Prevnar 13 include injection site reactions (i.e., erythema, swelling and pain) in addition to irritability, increased sleep and decreased sleep. Most injection site erythema and swelling was mild or moderate in severity; up to 20% to 40% of injection site pain was graded as significant. • No new safety signals were apparent in children 5 through 17 yrs of age.	• The safety profile of Prevnar 13 in children 6 through 17 years of age, based on data from study 3011, is acceptable. • There are no safety data in children 6 through 17 years of age who are at increased risk of IPD.
Risk Management	There are no new safety signals for PCV13 based on data submitted to this BLA supplement.	Routine pharmacovigilance is recommended.

11.4 Recommendations on Regulatory Actions

The data submitted to this BLA supplement provide evidence for the safety and effectiveness of a single dose of Prevnar 13 in children and adolescents 6 through 17 years of age for the prevention of invasive pneumococcal disease caused by the thirteen pneumococcal serotypes contained in the vaccine.

This submission fulfills the postmarketing requirement issued in the original Prevnar 13 approval letter dated February 24, 2010.

11.5 Labeling Review and Recommendations

CBER communicated with the applicant to achieve consistency with CBER's current guidance on the intent and format of package inserts. The final label was reviewed by the clinical team and found to be acceptable.

11.6 Recommendations on Postmarketing Actions

The Applicant agrees to carefully monitor for any unanticipated risks in ongoing clinical trials, surveillance systems of various countries, and postmarketing adverse reaction reports (i.e., routine pharmacovigilance).

A future study which evaluates, as a pre-specified objective, the impact on safety and immunogenicity of concomitant administration of Prevnar 13 with routine pediatric and adolescent vaccinations (including influenza vaccines) compared to Prevnar 13 administered alone could merit further discussion. Immunologic interference was observed when Prevnar 13 was administered concomitantly with inactivated trivalent seasonal influenza vaccine in older adults. Thus, further studies evaluating for any potential immunologic interference when Prevnar 13 is administered concomitantly with influenza vaccines in children 6 through 17 years of age could be of interest.